“Feeling Better Than Ever”

Are there any internally consistent responses to the challenge of ‘better than perfect’ human health enhancement technology in a health technology appraisal context?

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This thesis is submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy in Health Economics and Health Policy

This thesis is the work of Alex Bates and has not been submitted in substantially the same form for the award of a higher degree elsewhere.

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Abstract

Most modern publicly funded national healthcare systems (NHSes) make decisions about which technologies to fund and which to reject through the principles of health economics, and specifically the principles of 'Health Technology Appraisal' (HTA). Current HTA methods implicitly assume that health is anchored between zero (worst possible health) and one (best possible health), but the mathematics underlying HTA does not require this – mathematically the concept of 'better than perfect' health is entirely meaningful. However, to date there are no examples of technologies which actually create 'better than perfect' health and so the problem has never really been considered by health economists.

This PhD thesis proposes that human enhancements – technologies which can "modify basic parameters of the human condition, which were previously thought immutable" (Bostrom & Roache, 2008) – might be able to create 'better than perfect' health states, and traces some of the implications of this for NHSes under current HTA rules. The key observation is that there is no obvious practical limit to how much better than 'perfect' health could get, and therefore a risk that following HTA rules blindly could lead to an NHS becoming 'Subverted' – NHSes becoming vehicles for prescribing this wonderful enhancement rather than making sick people healthier. It is therefore critical that the NHS regulators – and most specifically HTA agencies – adopt a systematic approach to 'better than perfect' healthcare to prevent this outcome if they believe it to be unjust.

To begin to develop such a systematic approach, this thesis creates an economic theory of human enhancement and tests whether there is any approach which is consistent with all implications of this theory. The study draws heavily on interdisciplinary readings of the relatively developed bioethics literature on 'better than perfect' health and the health economic methods of health technology appraisal.

It is hoped that the results from this approach will inform the response of HTA agencies and other regulators to the emerging issue of 'better than perfect' healthcare technologies in a health technology appraisal context, as well as providing meaningful avenues of further research on the same topic.

Declaration

This thesis represents work undertaken for the Doctorate in Health Economics and Health Policy at Lancaster University Division of Health Research from January 2018 to May 2022. The work presented here is the author's own, except for ideas which are appropriately referenced in the text. This work has not been submitted for the award of a higher degree elsewhere.

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I am also indebted to various thinkers who have never met me but who have nevertheless motivated me to pursue a PhD. In particular, I owe a significant intellectual debt of gratitude to Nick Bostrom, Julian Savulescu, Peter Singer, Scott Siskind and Karl Claxton – their work is an inspiring reminder that just because an idea is heterodox it isn't automatically unimportant.

Thanks also to my very long-suffering partner, Kat. Immediately following submission of this thesis, I promise I will start work on all the jobs around the house I have been putting off for the last four years…

Finally, thanks to Angus, for keeping me company throughout the process. I hope you found your warm mat a meaningful enhancement.

Word count

Chapter	Word count (main text)	Word count (including references and appendices)	Running total
1. Introduction	1722	2300	1722
2. Theory	12,003	19,529	13,725
3. Literature review	8575	16,551	22,300
4. Economic modelling	10,259	20,520	32,559
5. Theory development	5232	8515	37,791
6. Conclusions	2018	2220	39,809
		TOTAL	**39,809**

Chapter 1. Introduction

1.1. Motivation

1.1.1. Enhancements will revolutionise the world

When the public think about 'human enhancements', it is typically in a negative context (Heinz, Kipke, Müller, & Wiesing, 2014) – for example in the context of sports doping (Miah, 2006) or academic dishonesty (Goodman, 2010). Ever since reading the works of philosopher Nick Bostrom – especially *The Future of Humanity* (Bostrom, 2009) - I consider this perception to be mistaken. In fact, I consider this perception to be almost myopic, and the motivation for this thesis is fundamentally the desire to communicate quite how radically and positively transformative enhancements could be.

In the Summer of 1964, The Beatles started experimenting with serious hallucinogenic drugs. They went on to produce nearly a dozen albums of seminal importance, some of which – such as *Rubber Soul* or *Revolver* - almost certainly could not have been made without the influence of significant quantities of mind-altering substances (Goodman, 2010). This upends the idea that enhancements are only for hollow or inauthentic cheating; in comparison to their earlier and less critically regarded albums such as *Please Please Me* and *Beatles for Sale*, it seems fair to say that much of the truly important work of The Beatles was only possible thanks to the horizon-expanding effects of LSD and its interaction with the unique and fragile creative pairing of Lennon and McCartney – LSD functioned as an 'enhancement' to a partnership already operating near the limits of human creativity, and allowed the pair to transcend those limits. It seems plausible that the enhancements which improve the ability to make rock and roll music will be different from the enhancements which improve the ability to cure cancer (Anonymous, 2009), solve the climate emergency (Lehmann, 2017) or explore deep space (Szocik, 2020), but nevertheless it seems equally plausible that if we could tackle each of the aforementioned problems with a cadre of scientists and politicians where Lennon/McCartney-level genius in the respective field was commonplace it would be one of the most important developments in the history of human civilisation.

However, even this Panglossian view of enhancements does not fully capture what is so exciting to me about them. A fundamental omission in the public debate around enhancements is a recognition that human enhancement technologies represent an opportunity to "modify basic parameters of the human condition, which were previously thought immutable" (Bostrom & Roache, 2008). Perhaps enhancements might enhance morality (Persson & Savulescu, 2019), deepen or create love between individuals (Ferraro, 2015) or create a new class of moral entity altogether – a 'post-human' (Lawrence, 2017). Naturally, such a potentially fundamental shift in our relationship to our own capacities has generated a lively and ongoing debate in the bioethics literature over how we should respond to enhancements. Bostrom and Savulescu (2009b) describes the emerging debate on these topics crystalising along "biopolitical fault lines", with 'transhumanists' adopting a view that self-modification is a fundamental right and 'bio-conservatives' taking the position that we should not fundamentally alter the human condition. Bostrom and Savulescu (2009b) also optimistically notes that there may be a brief window in which the debate can be productively carried into new areas by focussing on technical aspects of enhancements, of which I hope this thesis will be an example.

The reason I therefore think that this thesis is likely to be exciting and compelling – the reason I think it was worth me writing it and will hopefully be worth a reader reading it – is because I think enhancements will change the world, and it is fundamentally exciting to be performing research at the precipice of a revolution.

1.1.2. Enhancements and health economics

This work has a multidisciplinary focus between health economic and bioethics, based on the assumption that enhancements are likely to initially be presented to the public as of medical relevance. This is a reasonable assumption for at least two reasons:

- Insofar as enhancements exist today (we might call them 'proto-enhancements'), they are almost all regulated through the medical system. For example, vaccines might be said to enhance the immune system (Cooper, 2002), IVF technology might be said to enhance fertility (Bostrom & Roache, 2008) and prosthetics might be said to enhance certain motor

characteristics in certain contexts (Menuz, Hurlimann, & Godard, 2013). It seems logical that this method of regulation will continue to be the case, at least initially.

- A large and well-funded pharmaceutical industry exists which will be well positioned to undertake the research, development and regulatory filings associated with certain kinds of enhancement (Rajczi, 2008). This might, for example, be accomplished by 'condition branding' an ordinary unenhanced human experience as a particular kind of disease (D. Hall & Jones, 2008) and then enhancing this condition (a process which arguably happened with low libido, or 'hypoactive sexual desire disorder' as it was rebranded (Meixel, Yanchar, & Fugh-Berman, 2015)). The pharmaceutical industry is experienced at working within the medical regulatory system, and therefore there will be pressure from industry to extend the remit of the existing regulatory system to cover enhancements.

If this is the case, it will be for the medical system to set the context of society's response to these technologies, and specifically for health economists working within that system to make incisive and far-reaching decisions about how society should value a collection of potentially very diverse technologies (whether or not the medical system is *ultimately* the best framework to make these decisions in). It is not unfair to say that health economists as a profession have not always had a straightforward relationship with bioethicists (Claxton & Culyer, 2006; Harris, 2005, 2006), and so I believe that by positioning this project as a 'bridge' between the relatively developed bioethics literature on human enhancement and the powerful paradigm of health economics I may have identified one of Bostrom and Savulescu (2009b)'s productive areas into which to carry the debate. By spanning both literatures, this research project should provide a framework for more collaborative working in the future as well as producing results of importance to the NHS and its regulators more broadly.

1.1.3. Importance of health economic research into enhancements

When technology advances quickly, regulators can struggle to keep ahead of the technology they are supposed to be regulating (Moses, 2007). This is especially true of technological progress in biomedical sciences, where many technologies have the potential to create radically new regulatory

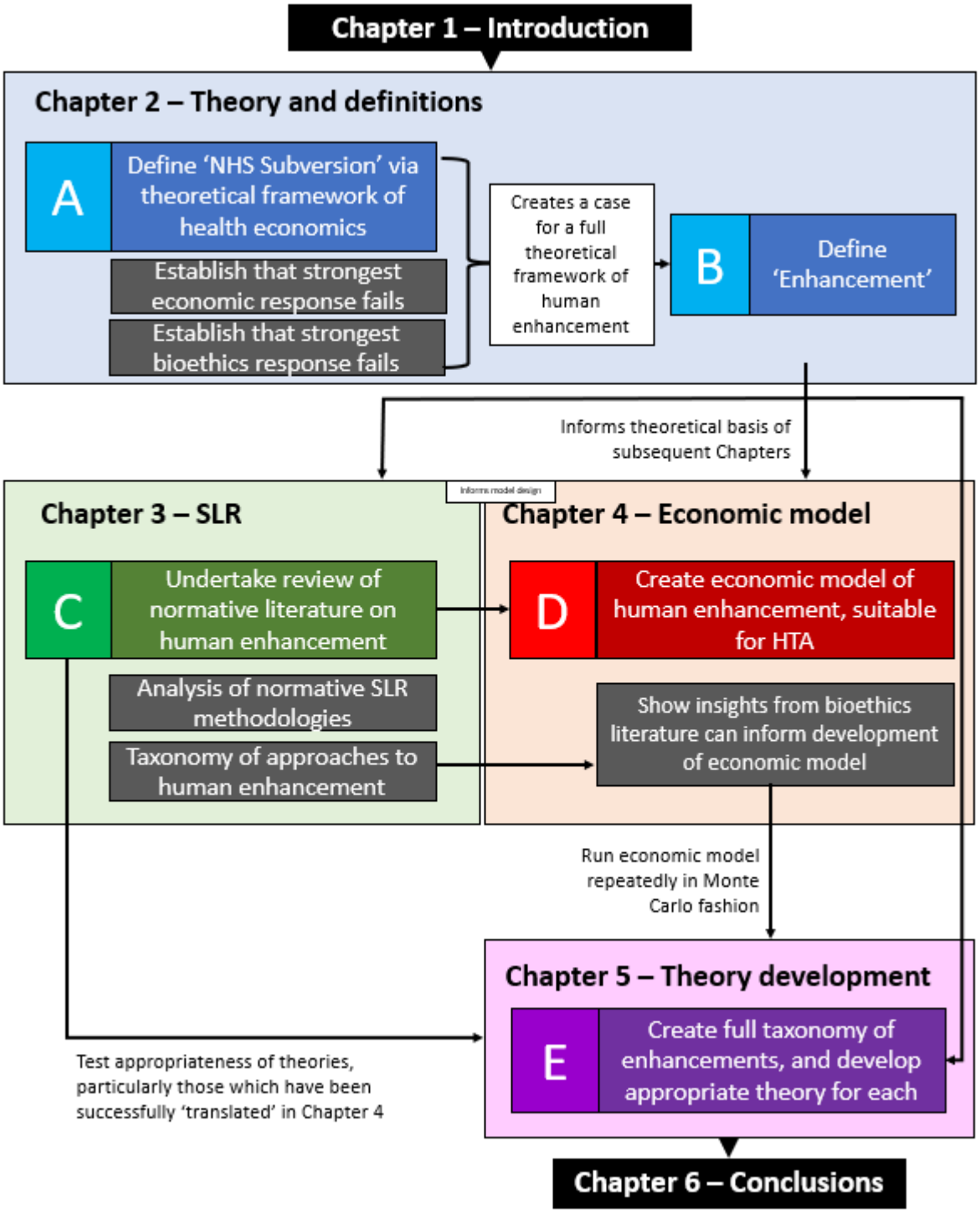
environments in a single step (Lev, Miller, & Emanuel, 2010; Moor, 2005). Fundamentally this research seeks an answer to the question of whether a consistent health economic theory of human enhancement, suitable for use by health technology assessment (HTA) agencies in assessing human enhancement technologies, can be developed, with the overall aim of supporting regulators in the challenge of remaining methodologically equipped to regulate a new and exciting class of medical intervention.

The impact of inadequate regulation is well characterised and can be harm to the public, a lack of public trust in the regulatory framework and a chilling effect on future innovation owing to an uncertain regulatory climate (Schneider, 2015) – for example if companies do not invest in human enhancement research because of fears that it may not be reimbursed if they do. However, this thesis argues that for enhancements in particular, the impact of inadequate regulation could be the gradual 'Subversion' of the healthcare system. Pessimists have been incorrectly predicting the end of publicly funded healthcare systems since the inception of the UK NHS (MacKillop & Sheard, 2018), but there are reasons to believe that enhancements "change the rules of the game" (Coeckelbergh, 2013) and the resilience of publicly funded healthcare in the face of increasingly sophisticated medicines and devices cannot assure us of a successful response to enhancements. Specifically, the possibility that enhancements can offer levels of health-related quality of life which are 'better than perfect' (assessed against current standards) could fundamentally change what kinds of health we value as a society, and how the healthcare system should operationalise decision-making in a post-enhancement environment.

1.2. The structure of the thesis

The goal of this research is to identify a set of coherent and internally consistent responses to the challenge of human enhancements in public funded healthcare systems. In order to achieve this, the thesis is split roughly into four conceptual elements, each occupying one Chapter for simplicity. Figure 1 shows how the different conceptual elements of the thesis are positioned in relation to each other.

Figure 1 – Conceptual diagram of the structure of the thesis



As Figure 1 demonstrates, the ultimate aim of the argument is to generate a taxonomy of responses to enhancement, and assess their suitability for enhancements of different kinds –Table 14 towards the end of the thesis is little more than a matrix summarising the possible enhancement/policy dyads. In order to generate this output and hence answer the question, each Chapter builds a relevant piece of the conceptual framework:

- Chapter 2 is a theoretical investigation of key terms, an important step in any research (van Mil & Henman, 2016). The Chapter is divided into three parts; the first defines 'NHS Subversion' in the context of a health economic framework, the second considers the best possible responses to the problem that do not require creating a health economic theory of human enhancement and – having concluded that a *de novo* health economic theory of human enhancement is in fact necessary – the third offers a working definition of the concept of 'health-related human enhancement'.
- Chapter 3 is a systematic literature review of key concepts related to 'health-related human enhancement', building off the definition given in Chapter 2. The Chapter notes some interesting and novel theoretical issues with performing systematic reviews on enhancement literature, before concluding that there does exist bioethics literature that contains relevant economic insight, but that this literature must be 'translated' into economic concepts via a more formal mathematical framework.
- Chapter 4 is the methodology and results of this 'translation' project – an economic model combining the conceptual paradigm of health technology assessment with the flexibility to consider the economic insights of the bioethicists identified in Chapter 3. Guided by the definitions from Chapter 2, the Chapter is divided into two parts; first explaining the methodology of the model and second performing the 'translation' of bioethics concepts into the model for later use.
- Chapter 5 offers the results of the project, applying the economic model designed in Chapter 4 to hypothetical future states derived from bioethicists' thinking identified in Chapter 3 and filtered through the definitions created in Chapter 2. The ultimate result is a taxonomy of possible enhancements, and an evaluation of how effectively different technical and policy responses might address each taxon.

Chapter 6 then offers some conclusions, summarizing the work done to date and highlighting future areas of investigation, especially those which will begin to be relevant as 'proto-enhancements' begin to get invented and approved by medical regulatory agencies.

Chapter 2. Towards a theory of health-related human enhancement

2.1. Chapter summary

The Chapter is the longest and arguably most conceptually complex in the thesis, and consequently a short summary of the arguments within is given below. Broadly, the Chapter consists of three parts:

1. Section 2.2 describes the problem of 'NHS Subversion', which was referenced in Chapter 1. 'NHS Subversion' is a process whereby enhancements which offer 'better than perfect' health' can force a publicly funded system to become an enhancement-delivering system with minimal or no activity centered on helping the sick. The UK NHS is used as an example of the way this process may unfold, since the UK NHS sets out its decision-making criteria particularly clearly.
2. Section 2.3 considers the strongest possible response to the problem of NHS Subversion, which is to argue that we can avoid the problem by appealing to notions which are 'common sense' in some fashion – specifically by arguing that the concept of 'better than perfect' health is in some sense contradictory or self-defeating. This section considers two arguments:
    - Mathematically (that is, to a health economist) the concept of 'better than perfect health' is meaningless because the best achievable health is always anchored to 'perfect' in health economics.
    - Philosophically (that is, to a bioethicist) it is possible to draw a clear distinction between enhancements and therapies, meaning that it is possible to ensure the NHS is protected from NHS Subversion by – for example – refusing to fund enhancements with 'subverting' properties.
3. Having concluded that the strongest possible counterargument to NHS Subversion fails in Section 2.3, Section 2.4 defines the key conceptual term which will underpin this theory ('health-related human enhancement') in a way that makes sense given the challenges presented by NHS Subversion. The resulting definition is a reasonable 'working theory' of enhancement.

2.2. The problem of NHS Subversion

2.2.1. Introduction

The problem of 'NHS Subversion' is the key motivating force behind this thesis. It sets out the case that using a perfectly conventional interpretation of ordinary resource allocation rules, a publicly funded healthcare system could drift from providing mostly healthcare to providing mostly enhancements, meaning that a healthy person desiring – for example – a bionic eye to improve their tennis game could be prioritised for publicly-funded treatment above a sick person requiring lifesaving chemotherapy.

As discussed in Chapter 1, it makes sense to refer to all publicly funded healthcare systems as 'NHSes' by convention for brevity, and to explicitly distinguish between the abstract concept of a centrally-planned and coordinated publicly funded healthcare system and the specific instantiation of the UK NHS only where appropriate to use as an example. Broadly speaking, this section defends the claim that NHSes have a particular theory of health and that (certain kinds of) enhancement causes a significant problem for it.

2.2.2. The health technology assessment framework

Whether publicly or privately funded, all healthcare systems are resource constrained, meaning they have more projects available to fund than money available to fund those projects (Laing & Shiroyama, 1995). While privately funded systems (or the privately funded elements of mixed systems) can resolve this dilemma by using market mechanisms like price to allocate resources efficiently given this constraint, publicly funded systems (or the publicly funded elements of mixed systems) must use a different design if they are to accomplish their goals. In general there are many ways to design a healthcare system around a hard resource constraint, but almost all publicly funded healthcare systems attempt to distribute resources in line with some conception of the common good as understood through social value judgements (NICE, 2008).

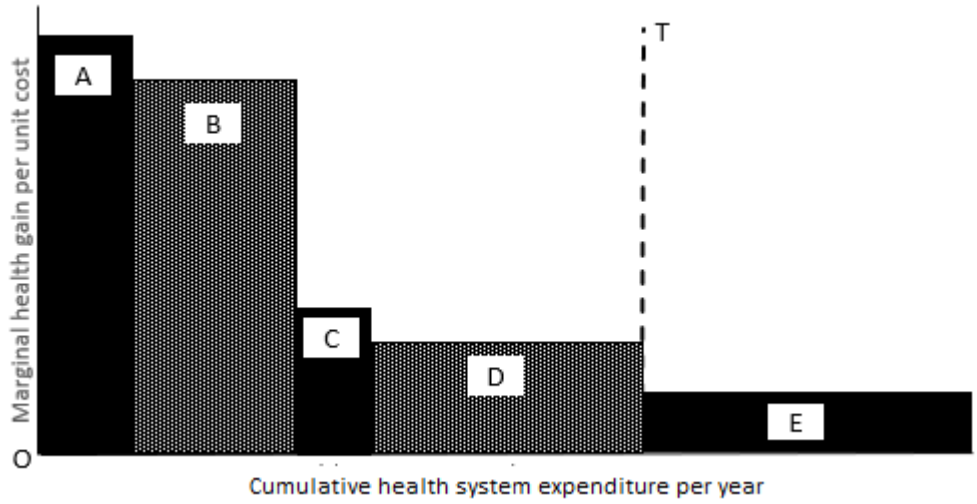
The mechanism by which this is accomplished would be recognise by ethicists as an example of a consequentialist outcome framework (Carr-Hill, 1991); it does not matter who receives what benefit at what price, as long as society cannot arrange matters such that society in aggregate can have more of the desirable outcomes for the same allocation of resources. This means that the NHS may devote

itself to treating relatively inconsequential diseases provided that the cost of doing so is sufficiently low (A. Smith, 1987), which is the critical observation that caused the problem described later.

The health outcome which is to be optimised varies between NHSes – for example the system might try to optimise life expectancy of the population, years lived in good health or some more complicated algorithm weighting length and quality of life (MacKillop & Sheard, 2018). In the UK NHS the measure used is the Quality Adjusted Life Year (QALY), "[a] measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life" (NICE, 2013). Practically, what this means is that the QALY is a combined measure of length and health related quality of life, such that 'one QALY' is always equivalent to one year of life lived in perfect health (for example, two years of life lived at a health state half as good as perfect would be equivalent to one QALY (see for example McCabe, Claxton, and Culyer (2008)). The QALY is exclusively discussed from this point onwards since it is most discussed in the health economics literature, but the argument would follow exactly from any measure of health outcome an NHS might realistically try to optimise.

In an idealised mathematical model of healthcare decision making the system would identify the most marginal technology it currently funds (i.e. the one with the highest incremental cost-effectiveness ratio (ICER), or – colloquially - 'the least cost-effective') and refuse to fund technologies less efficient than this, making the system more efficient over time (Weinstein & Zeckhauser, 1973). This creates a 'threshold' for healthcare spending decisions (Culyer et al., 2007). This idealised model is illustrated in Figure 2, which shows five treatments A through E arranged in order of cost-effectiveness (calculated as the marginal health gain per unit cost), where their width is the absolute impact they have on the health system budget. The diagram also shows dotted line T, representing the budget of the health system. After spending money on treatments A, B, C and D the total spend is equal to the budget and treatment E cannot be afforded. If a new treatment – F – was introduced into this system, it would have to be at least as cost-effective as treatment D in order to lie on the left hand side of line T, and would displace part of treatment D in order to ensure it was funded. Therefore, the cost-effectiveness of treatment D represents the 'ICER threshold' in this idealised system.

Figure 2 – Illustration of an idealised mathematical model of healthcare decision making



In practice the challenges of representing the full social value of a new technology in a mathematical fashion are significant (Collins & Latimer, 2013; Ferner, Hughes, & Aronson, 2010; McCabe, Claxton, & Tsuchiya, 2005), leading most systems to deviate slightly from the idealised mathematical model of thresholds presented in Figure 2 – the UK NHS is used as an example throughout this thesis due to an unusual willingness to candidly specify the tradeoff it makes in public, but even the UK NHS does not officially have a hard threshold; their health technology assessment regulators, NICE, write: "NICE has never identified [a threshold] above which interventions should not be recommended and below which they should" (NICE, 2008), although there is excellent evidence that decisions are unofficially made to an approximately £20,000 - £30,000 threshold (Devlin & Parkin, 2004).

Note that whether this threshold value is 'correct' in the sense of maximising the objectives of the NHS is an important policy debate (Towse, Pritchard, & Devlin, 2002), and the £20,000-£30,000 the UK NHS uses has been criticised as being both too high (Claxton et al., 2015) and too low (Towse, 2009) – for the purposes of describing this conceptual problem all that matters is that publicly funded systems like the NHS behave as though they have an approximate threshold in mind when making decisions about funding technologies, not the specific level of that threshold or the consistency with which it is enforced.

2.2.3. Consequentialism and healthcare utility monsters

The consequentialist position of HTA bodies is often summarised in the health economics literature as "a QALY is a QALY is a QALY" (Weinstein, 1988), which captures the notion that all QALYs are alike, however they are generated. Where exceptions to the threshold value exist, they are justified on the grounds of exceptional societal interest in promoting equitable outcomes otherwise unattainable at that threshold – for example when the condition affects very few patients per year and therefore developing the treatment would be economically unviable without charging higher prices (McCabe et al., 2005). Outside of these special circumstances, no conventional medical technology in the UK should cost more than the threshold per patient per year (NICE, 2008) since spending more than the threshold would imply the technology offers 'better-than-perfect' health of more than one QALY per year (that is, offers a health state people would prefer to one year of perfect health).

Like all consequentialist moral frameworks, consequentialist health resource allocation frameworks are vulnerable to a number of criticisms (Folland, 1986; Scheffler, 1988). For example, an inability to prioritise treatment based on equity concerns (Whitehead & Ali, 2010) or an inherent tendency to disfavour disabled people (Harris, 2005). According to Harris, disabled people have the 'double jeopardy' of both a disability causing them to gain fewer QALYs from each year they are alive and the healthcare system underserving them relative to fully-abled individuals precisely *because* they gain fewer QALYs from each year they are alive (Singer, McKie, Kuhse, & Richardson, 1995). These objections are well characterised, both within the broader ethics literature and the healthcare literature specifically. Alternatives to consequentialist frameworks – such as deontological imperatives to treat identifiable individuals in immediate need of help (the 'rule of rescue') have other characteristic drawbacks (Cookson, McCabe, & Tsuchiya, 2008).

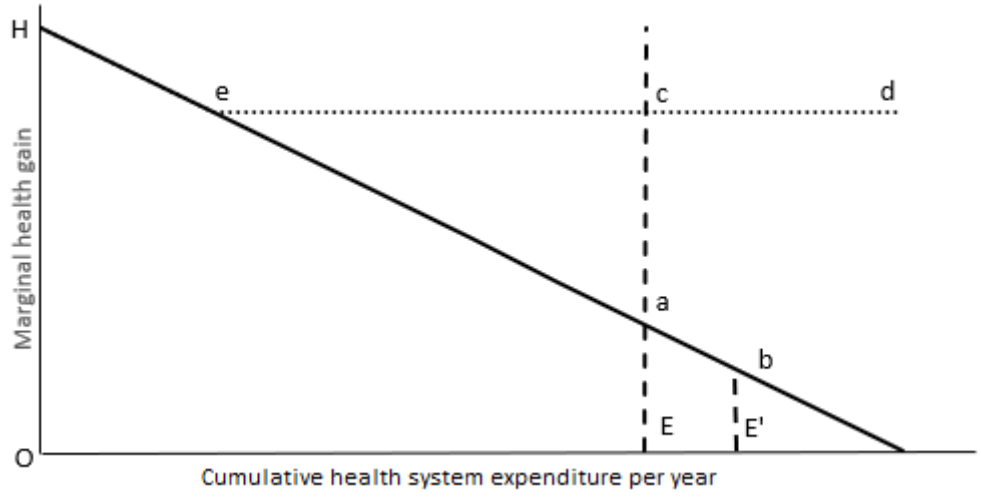
One specific problem with consequentialism which is less well characterised in the healthcare ethics literature is that of the 'utility monster'. The utility monster will "get enormously greater sums of utility from any sacrifice of others than these others lose" (Nozick, 1974), and the implication is that consequentialism demands we must sacrifice all of our happiness to the monster in order to increase total happiness in the world. It has been observed that healthcare resource allocation is as vulnerable

to a utility monster as any other consequentialist framework (Folland, 1986; Tannsjo, 2019), but the actual implications of finding such a monster have not been traced out in the literature. It is important to note that the phrase 'utility monster' invokes vivid images of – for example – a majestic dragon-like creature sitting on a great horde of stolen utility, when in fact the most philosophically challenging formulations envisage the monster as the unwanted output of a constrained system misallocating resources – this paper describes a monster of this less exciting (but no less important) type. For example, Parfit (1984) describes a 'repugnant conclusion' where for any given level of total happiness there is an equal or greater level of total happiness reached by a much larger population of people with significantly worse lives.

2.2.4. The implications of a utility monster

The potential impact of a utility monster on a publicly funded healthcare system is demonstrated in Figure 3, using a framework adapted from McCabe et al. (2008).

Figure 3 – Potential implications of a utility monster in a publicly funded healthcare system



In Figure 3 the solid line *Hea* represents the health system expenditure as it currently is – the '**conventional scenario**'. Treatments are purchased in decreasing order of efficiency per unit cost until the budget threshold *E* is reached, as per Weinstein and Zeckhauser (1973). If the budget were increased to *E'* the line *Heb* would represent health system expenditure – the overall health added to the system would increase, but the health added at the margin would have decreased, as the system could afford less efficient interventions.

The dotted line *Hec* represents health system expenditure using the same philosophical assumptions but with the addition of a utility monster which receives constant (high) returns to resources invested in it – the '**monster scenario**'. This scenario necessarily means the monster has 'better than perfect' health since there is a finite amount of ill health in a given health economy and therefore returns could not be constant under any other circumstance. Line *He* represents health technologies which would have been purchased in any case – technologies which are so efficient they have negative or near-zero cost per QALY, for example. Line *ec* represents healthcare spending on the utility monster. Far past point *d* the marginal health benefit may begin to dip if the monster is satiated and interventions as described in line *ea* become the next-most cost-effective. As with the conventional scenario, the NHS can only fund treatments up to their budget constraint *E*, but unlike the conventional scenario increasing the budget to *E'* will not decrease the marginal health gained per unit spent, because the utility monster benefits equally at the margin under budget constraints *E* or *E'*.

The problem is plain to see from this diagram; under the conventional scenario, the total health generated is given by the polygon *OHaE*. This is clearly less than the total health generated under the monster scenario, which is *OHecE*. The reason this is 'clear' is that the triangle defined by points *eca* is marginal improvement for the monster scenario compared to the conventional scenario. Therefore, the health system should prefer the monster scenario to the conventional scenario. However, the cost of gaining these improvements to the total health generated is that the healthcare system becomes effectively a monster-feeding system – almost all healthcare activity is devoted to the monster and the monster alone, and healthcare of the conventional kind that society expects only occurs in a meaningful sense under the conventional scenario.

2.2.5. Enhancements and NHS Subversion

An important conceptual point of this argument is that there are many mathematical oddities in health economics which nevertheless do not trouble regulators day-to-day. The Keeler-Cretin paradox proposes that under certain circumstances it is never right to invest in public health interventions because it is always more efficient to wait one more day to implement the intervention (Keeler & Cretin, 1983), but regulators – very pragmatically – appear to take the view that those assumptions

must not hold in practice. The phenomenon of 'unrelated future costs' may imply that saving a child's life at any price is cost-ineffective because diseases of old age are so expensive (Morton et al., 2016); again, regulators tend to disregard this theoretical effect since it is so out of alignment with the commonly-understood purpose of the healthcare system, and indeed in the UK NHS it is explicitly forbidden to consider unrelated future costs in health economic analysis (NICE, 2013).

Therefore discovering that the NHS is vulnerable in theory to utility monsters is not an important finding (or even especially novel – see Tannsjo (2019)). What matters is that the NHS is not practically vulnerable to such problems if the current scope of NHS activities precludes most utility monsters from occurring in practice. For example, in the UK NHS, Parfit (1984)'s objection would not be relevant, since the UK NHS (along with most other publicly funded healthcare systems) adopts a position that they aim to "make people happy, not make happy people" (Narveson, 1973) and that therefore they are not committed to expanding the population of their host country at all costs, as Parfit argues they might be under some operationalisations of consequentialism. The conceptual framework which allows NHSes to be confident that they are not vulnerable to such monsters is the idea of 'perfect health' being a satiation point for healthcare spending; the most radical treatment we could imagine – a treatment which took someone from the brink of death back to perfect health – would not function as a utility monster because upon reaching perfect health the patient's health-related utility function would be entirely satisfied and require no more resources.

The key and critical difference of human enhancement is that they may serve to "change the rules of the game" (Coeckelbergh, 2013) and provide a situation where individuals do in fact have utility functions which cannot be satisfied by any finite amount of resources. A very simple example of human enhancement with high economic relevance is life extension technology. This technology is currently in its infancy and spans a number of possible modalities (S. S. Hall, 2003). Nevertheless, it is already recognised as an area where a major breakthrough could have profound effects for society (Bartlett & Underwood, 2009). Consider a technology which extends the life of an otherwise healthy person by some amount for a fixed cost, and can be given repeatedly (for example, a treatment given once a year that extends life by one year). The effect would be a 'sink' for healthcare spending exactly

as described in Figure 3; as soon as the cost per additional QALY of this technology was cheaper than the next most marginal therapy, the entire remaining healthcare budget would be devoted to it and still the individual would not have had their utility function satisfied.

In principle, therefore, publicly funded healthcare systems are vulnerable to consequentialist utility monsters by virtue of the economic consequences of resource scarcity. While all known healthcare systems have been able to resist all known potential utility monsters up until now, enhancements are effectively an 'unknown unknown' which could be introduced into this system. We should therefore be concerned with whether enhancements will inevitably Subvert every healthcare system they interact with, or whether there is scope to protect those systems from the utility monster enhancements create.

2.3. Responses to the problem of NHS Subversion

2.3.1. Introduction

The problem of NHS Subversion only exists because we assume that an enhancement could be invented which will function as a kind of utility pump, endlessly generating QALYs for as long as we feed it resources. Of course, it is possible that such an enhancement might never be invented, perhaps because it is too difficult or cost-prohibitive to engineer in practice (like a flying car). However, the strongest argument against the NHS Subversion problem is that such an enhancement literally *cannot* exist in any possible world (like a triangle with four sides). This would ensure that the NHS cannot possibly be Subverted, and therefore indicate that the NHS can respond to enhancements without any particular risks. In this section, two arguments are considered which if accepted would prove that Subverting enhancements could not exist:

- An economic argument that quality of life is anchored to 1 at the top end, and therefore claims about interventions that give >1 QALY per year are meaningless.
- A philosophical argument that enhancements can be cleanly distinguished from ordinary medicine, and therefore if there is ever a risk of an NHS becoming Subverted, that NHS can simply stop funding the problematic enhancement.

As an important aside, there are also a few radical responses where more fundamental assumptions in the NHS Subversion framework are abandoned – for example perhaps policymakers could conclude that the NHS should be disbanded in order to prevent it being Subverted, which would – clearly – prevent the NHS spending public money on enhancements. A more reasonable position one could take is that perhaps we might say that the NHS *should* in fact allow itself to become 'Subverted' and QALY maximisation at all costs is an opportunity to enhance human well-being on aggregate even if it seems individually repugnant to us – a position associated with Singer's defence of many apparent contradictions of consequentialism (Singer, 2019). For the sake of offering the most robust argument possible I assume - for now - that the public in general are approximately happy with the social value judgement embodied in their NHS and therefore would not accept Singer-like levels of commitment to biting challenging consequentialist bullets – however this assumption is relaxed in Chapter 5.

2.3.2. Response 1 - Health states must be anchored at 1 (the economic response)

2.3.2.1. Outline of the response

The 'textbook' treatment of health in health economics is to describe health-related quality of life as a function of health (which might be made up of many subdomains such as mobility, pain, mental health and so on – see Kind, Brooks, and Rabin (2005)), and then smoothly map that function to a utility scale running from 0 (the worst health imaginable, i.e. 'death') and 1 (perfect health) – see for example Torrance (1986). This results in the situation, described in Section 2.2.2, where the NHS will never pay more than a threshold level for any given treatment. If this treatment is correct, then a Subverting enhancement is impossible in principle; better than perfect health requires that quality of life in a given period be greater than 1, and part of the definition of health is that it cannot be greater than 1. Therefore, the existence of a better-than-perfect health treatment would create a logical contradiction (like asserting you had discovered a particular kilometre that contained more than 1000 metres).

An objection here is that the it is completely arbitrary to refuse to treat an obvious enhancement as an enhancement just because it causes problems for health economists' definitions. More 'creativity' clearly enhances humans along domains we consider relevant to their flourishing (Farah, Haimm,

Sankoorikal, & Chatterjee, 2009), and to refuse to acknowledge this is churlish. This objection can be cleanly defeated however: the NHS, in general is concerned only with *health-related* quality of life, whereas people generally are concerned with quality of life in a more holistic sense (sometimes described in the philosophical literature as 'well-being' (cf. Hooker (2015)). Health is a component of a well-lived live, but is not constitutive of a well-lived life. For example; risky sports (Nutt, 2009), protesting authoritarian regimes (Ong & Han, 2019) or joining religious groups that forbid the use of certain modern medical technologies (Mitchell et al., 2012) might all be examples of taking risks to lifetime expected QALYs for a payoff measured in non-QALY benefits. Similarly, we might say that certain health interventions create benefits both in the 'health' domain and in some other domain. In the example above, enhancing creativity might help in the health domain of treating depression related to life feeling too similar day-to-day, but also might help in the non-health domain of writing really good philosophy papers. On this schema, once you have obtained health-related quality of life = 1 ('perfect health'), you know by definition any other benefits the intervention gives you at the margin must be non-health, and this makes the exact magnitude of these benefits outside the domain of the NHS (that is, the response the NHS should adopt to enhancements is to treat them as giving a flat quality of life of 1 exactly in the health domain, no matter how spectacular their effects in other domains).

Publicly funded healthcare systems do not always perfectly embody this principle. For example, the UK NHS has experimented with 'social prescribing' in recent years, when it is thought the root of a medical problem might lie in socioeconomic or psychosocial causes (Brandling & House, 2009). This would imply that the UK NHS (at least) considers that the relevant domain for its interventions might be somewhat larger than 'classically' health-related interventions. Furthermore, the UK medical regulator, NICE, has issued guidance where the relevant perspective considered included the education system (NICE NG93, 2018) or criminal justice system (NICE NG66, 2019), indicating that in principle the value assessment of a health-related technology does not need to be strictly confined to health-related outcomes. Nevertheless, it is reasonably fair to say that appealing to this principle explains the majority of NHS behaviour the majority of the time – again using the UK NHS

as an example we see that the UK NHS will offer smoking cessation advice unprompted in certain situations (Bauld, Bell, McCullough, Richardson, & Greaves, 2010) despite the fact it could be argued that the smoker is merely engaging in a risky activity that enhances their overall well-being at the expense of their health. It is reasonable to conclude that there is an internally consistent response to enhancements if the NHS can simply choose to ignore them if it wishes.

2.3.2.2. Problems with the 'textbook' treatment of QALYs

Although the above response neatly resolves the problem of NHS Subversion in a 'textbook' sense, any practicing health economist knows there are several mechanisms by which the NHS might end up paying more than the threshold value per QALY for a treatment. For example:

- Non-standard perspective – In particular, a societal perspective, if relevant, could mean that the value to society of treating a particular condition is greater than the value of treatment to that individual in purely health terms (NICE, 2013).
- Multiple beneficiaries of an intervention – Where the intervention affects more than one person, it is possible for one intervention to give more than 1 QALY per year. This most commonly occurs with public health interventions which affect many thousands of people, but might also occur if e.g. a paediatric medicine also relieves burden on the child's parents / carers (NICE, 2013).
- Social value judgements – For example treatments for very rare diseases are sometimes granted an explicitly higher cost-per-QALY threshold (NICE, 2008) or informally given precedence over more conventional medicines. This is to recognize the significant social value associated with treating these diseases.
- Epistemic uncertainty – Where the intervention is expected to add some number of QALY based on the results of a clinical trial, but in fact the trial gives a misleading impression of effectiveness and in fact the treatment is less effective than this.
- Historically contingent HTA elements – Where a treatment was approved under certain conditions, and those conditions later change. For example, a PDL-1 inhibiting cancer treatment might be approved on the basis of being cost-effective compared to a cisplatin-only

regimen of chemotherapy, and this guidance might not be updated when clinical opinion changes to prefer a superior Cisplatin-Lomustine-Vincristine regimen.

- 'Worse than death' health states – Where the disease (pre-treatment) is so bad that it affords negative health-related quality of life, and therefore the treatment can add arbitrary quantities of QALY by taking health from some negative value to 1.

Interventions with characteristics that exploit any of these characteristics to Subvert the NHS could be developed, although some are clearly more likely than others (for example, in order for the NHS to become Subverted by epistemic uncertainty a systematic misrepresentation of trial data bordering on fraud would have to be sustained for many decades). Of the list presented above, however, 'worse than death' health states are clearly the most relevant to this discussion since they form the obvious mirror of the 'better than perfect' health states which drive the basic Subversion model in Section 2.2.

The next section describes how the developed literature on 'worse than death' health states can apply in the context of 'better than perfect' health states

2.3.2.3. 'Anchors aweigh'

There is a developed theoretical and empirical literature on the 'anchor state' at zero (which is conventionally understood to be death (Torrance, 1986)) and therefore it is possible to use much of this thinking to inform consideration of 'perfect health'. Sampson, Parkin, and Devlin (2020) argue that the use of zero as an anchor state in health economic evaluation is problematic. In doing so they raise a number of important issues which also apply to the use of one as an anchor state.

There is considerable value in having universally agreed reference states in health economic analysis (Kaplan & Ernst, 1983). These reference states 'anchor' the range of health states a human can experience and so allow for the expression of health as a relational rather than absolute concept (Schroeder, 2013). For example it does not make sense to say someone has 'four units of tall' but rather to say that someone is 'taller than average' (Schroeder, 2013), and it may be helpful to think of health in the same way. Obviously, another way of solving this issue would be to create an unambiguous scale of health measurement analogous to measuring height in metres or feet, but it may

be ‘helpful’ in the sense that it makes mathematical operations on the resulting concept must be more straightforward (Torrance, 1986) and that it fits neatly with the axioms of expected utility theory (Fishburn, 1970) (and more importantly, instruments built off those axioms like for example the Standard Gamble (Dolan & Sutton, 1997)). Another valuable property anchors may serve is in translating philosophical into mathematical concepts. For example, Sen (1974) defines health in terms of functional capabilities, and therefore sees death as maximally dysfunctional which is perhaps philosophically distinct to Glackin (2019) who defines health as a socially constructed phenomenon and therefore sees death as being the state most agreed to be worth avoiding. By anchoring health states to zero and one we can ensure that these contestable terms are rigorously defined within an economics context.

In some ways death has the perfect properties for an anchor state, since death affects everyone equally, affects every possible domain of health and is completely irreversible (Goldsmith, 1972) (this is perhaps not unarguably true since people may fear death for reasons other than the impact on their health, such as the loss of time in which to complete important projects (Fanshel & Bush, 1970)). Nevertheless, compared to the concept of ‘perfect health’ which is a highly complex and culturally specific notion (Sullivan, 1966), the concept of ‘death’ is a very convenient anchor.

However, since the development of the foundational theories of health economics, the concept of a health state worse than death has become widely accepted (Torrance, 1984). An example of a health state worse than death is being completely reliant on a breathing machine, which 66% of stroke patients agreed would be indistinguishable from or worse than death (Everett, Everett, Brier, & White, 2021). There is some evidence that these health states worse than death are more uncommon in real life than mathematical models might suggest – interviews with patients judged to be in a health state worse than death do not tend to show that they regard their own life as not worth living (Bernfort, Gerdle, Husberg, & Levin, 2018) and there is some evidence that people may not understand the methods used to elicit health state utilities when applied to extreme examples like states worse than death (Van Nooten, Koolman, & Brouwer, 2009). However, the overwhelming consensus in the literature is that health states worse than death do exist, and there is at least anecdotal evidence of

mentally competent people choosing to die rather than live out health states they expect to be unpleasant (Dyer, 2013). Therefore, even if heath states worse than death are rarer than the raw numbers might suggest, there only needs to exist one health state which is genuinely worse than death in order to prove the existence of health states worse than the zero anchor, and therefore demonstrate that the concept of 'health' as it is actually used by the NHS does not anchor at zero.

Sampson et al. (2020) give several credible reasons why anchors at zero are not necessary, which apply equally well to anchors at one. For example, an anchor is not needed to calculate change in health state, which is all that is needed for conventional health economic analysis. Clearly, not all arguments will apply in all situations - Sampson et al. (2020) point out that it is not obvious that we should regard death as a state relevant to health (analogising it to other unpleasant states which can be a result of ill-health, like unemployment) whereas it is clear by definition that 'perfect health' must be a state relevant to health. However, by far their strongest argument is the existence of health states worse than death, proving that anchors are not necessary to conduct accurate health economic analysis.

Therefore, I conclude that the state of the art in the literature is that there is nothing special about the anchors chosen for health economic evaluation, other than their undeniably convenient mathematical properties (Torrance, 1986). Therefore, it can be understood that the expression 'perfect health' in textbook treatments of health economics is not making any special claim about what health is or what humans value – it merely represents one particular point on a continuum of the worst and best possible health which has been adopted as especially helpful for economists dealing with ordinary human variation (which most health economists do, but this research does not). Section 2.3.2.2 demonstrates that there is nothing particularly special about paying more than the threshold value for unusual treatments which offer more than the normal number of QALYs, and therefore I conclude that the objection described in Section 2.3.2.1 fails; there is no logical contradiction between existing health economic methods and the existence of health-related enhancements offering 'better than perfect' health. Indeed, the arguments of Sampson et al. (2020) suggest in fact that it is those

asserting the existence of such a contradiction who create logical inconsistencies, by insisting on an anchor state which does not really exist.

2.3.3. Response 2 – Enhancements and therapy can be clearly distinguished (the bioethics response)

2.3.3.1. Outline of response

The problem of NHS Subversion exists because we suppose the NHS will continue to blindly follow its existing rules even to the point that it Subverts itself. A very simple response to the problem of NHS Subversion is therefore to claim that all possible Subverting technologies can be recognised, distinguished from non-Subverting technologies and then some second set of rules written and followed for these Subverting technologies. This, therefore, raises the possibility of a bioethicist-led response to the problem of NHS Subversion – if therapy can be precisely distinguished from enhancement, then at the very least the NHS can always and forever avoid becoming Subverted by simply banning all enhancements (because all realistic candidates for Subverting technologies are also enhancements). It may be that a more sophisticated set of alternative rules would allow the NHS to avoid Subversion while still enjoying access to certain non-Subverting enhancements, but for the purposes of this thesis the strategy of 'ban all enhancements' would clearly resolve the problem of whether any possible approach could prevent Subversion, and do so in a way that leaves the NHS in no worse a position than it was pre-enhancements.

Although the concept of Subversion is novel in this thesis, the philosophical difficulty with distinguishing 'therapy' (that which treats disease and is the proper domain of the NHS) from 'enhancement' (that which enhances healthy people and is not necessarily the proper domain of the NHS) is very well explored in the literature (Erler, 2017; Holtug, 2011; Tengland, 2015). Naively, we might expect the therapy / enhancement distinction to be easy to draw in practice, since some of the more outlandish potential uses of enhancement described in Chapter 1 are the stuff of contemporary science fiction. However, the role of enhancement in the NHS is likely to be hard to define in practice, since many (if not all) near-future candidates for enhancement also serve some other unequivocally medical purpose (Bostrom & Savulescu, 2009a). Consider for example the drug methylphenidate (Ritalin®), which can assist an individual who needs to focus on a repetitive task for a long period of

time by stimulating the central nervous system and preventing fatigue (Sherzada, 2012). This has clear therapeutic value in the treatment of conditions such as attention-deficit hyperactivity disorder (Sherzada, 2012), but can also be abused by healthy individuals in cognitively demanding roles requiring sustained attention (Jalilian et al., 2013). The dual use of this kind of therapy now "beckon[s] as an instrument of improvement and consumer choice" (Sandel, 2012), which Sandel argues is not the purpose of healthcare.

Nevertheless, the mere fact that it is not simple or straightforward to distinguish therapy and enhancement does not imply that no such distinction exists. Juengst (1997) describes enhancements as a "boundary concept" that can help demarcate medical from non-medical social projects, and therefore we should perhaps expect that distinctions will become difficult when considering enhancements. Therefore, instead of relying on the existing definition we must theorise a definition of 'health' from first principles. Under typical circumstances, this would be extremely challenging - ordinary language offers some indication of what it is to be 'healthy', but is imprecise and heterogenous (Tengland, 2015) and many excellent philosophers have found defining health to be extremely complex (Boorse, 1997; Cooper, 2002; Schroeder, 2013). It is important to understand however that this research project aims at a much more straightforward target, which is to fit a theory of health-related human enhancement to existing HTA methodology such as that described by McCabe et al. (2008), and therefore 'health' as defined in this research project may be an entirely artificial construct; we are not interested in 'health' *per se*, but rather the sorts of things which the health system is interested in treating, which (we hope) maps onto the social value function society assigns to the health-related elements of human flourishing.

For conceptual clarity, the term 'disease' will be used throughout this section to refer to any example of non-health, and so therefore encompasses true diseases, disorders, malignancies, insults and so on.

2.3.3.2. Problems with existing conceptions of health

The most prevalent definition of health is usually presented as the one given by the World Health Organisation (World Health Organisation, 1948):

Health *is "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity."*

This definition was radical when it was first formulated in 1948, since it included multiple domains of what we now recognise as health (especially mental health) and demonstrated incredible ambition for the role of healthcare (Jadad & O'Grady, 2008). Nevertheless, the definition is not without issues (Huber et al., 2011; R. Smith, 2008) – the requirement that the state of health be "complete" implies a binary definition of health that "would leave most of us unhealthy most of the time" and therefore fails to map onto the actual activities conducted by NHSes, and the changing nature of healthcare in the modern world (more aging and chronic conditions) may mean that our understanding of what it is to be 'healthy' will have to change along with the definition.

Broadly, there are three conceptions of health described in the literature (Sartorius, 2006). These are summarised in Table 1 below, and a detailed and referenced discussion of each is given as supporting evidence in Appendix A.1.

Table 1 – Summary of three accounts of health

	Biological account	**Functional account**	**Social account**
Summary	Health is having no biological basis for the body underperforming	Health is being able to do certain activities associated with a flourishing life	Health is a particular kind of social process
Ontological paradigm	Realist	Realist	Constructivist
Epistemological paradigm	Empirical	Empirical to Constructivist depending on author	Interpretive
Relational class (where do we locate 'health' when we look for it?)	The behaviour of individual organs, or possibly even finer biological units (specific gene variants, for example)	Other individuals (including hypothetical idealised individuals)	Social constructs of the nature of health
On what continuum are health and enhancement located?	Both include interventions to lower the predisposition to negative outcomes	Both refine functionality to allow more / better activities	Both represent activities which could be performed by the health service of a society
Key author	Boorse (1975)	Sen (1974)	Glackin (2019)
Why is a broken bone an example of ill health?	Bones should provide structural support to the body without pain,	It causes functional impairment and pain – breaks that don't do	Society agrees that broken bones are pathological

	Biological account	Functional account	Social account
	and broken bones don't	this such as hairline metatarsal fractures are not examples of ill health	
Example of disease that causes problems for this account	Pregnancy (NICE CG62, 2019) – Pregnancy is not a malfunction, but is clearly an important medical event in its own right	Deafness (NICE TA566, 2009) – At least some people would argue that deafness does not alter functional ability to 'use language' (Cooper, 2007)	'Shell-shock' (now called Post-Traumatic Stress Disorder (NICE NG116, 2018)) - was not recognised as a disease in World War I (Babington, 1990)

All three conceptions of health fail to reach a conclusive position on the nature of enhancements and health. This is probably not surprising – the last row of Table 1 demonstrates that there are some significant flaws with each account which do not even rely on the philosophical complexities of enhancement. Appendix A.2 describes more criticisms of the three accounts as background to the specific discussion on enhancements which follows.

It might be argued that there could still be some mixed approach where – for example – the biological model is used for physical disease and the social model for mental disease. That is to say, in order to salvage a distinction between therapy and enhancement, we might conclude that we have several overlapping and competing concepts of 'disease', but which nevertheless are all nonoverlapping with any particular concept of enhancement. However, this approach does not seem complete either. For example, Cooper (2002) writes that a disease is something which is bad to have, which is unlucky to acquire and which can potentially be treated medically. However, even a sophisticated mixing the three accounts together in this way admits of exceptions; Cooper notes that her own account would consider unwanted pregnancy a disease, which would not be a normal way of understanding why an unwanted pregnancy is a bad thing.

It is possible to simply bite the bullet and assert that all of these peculiar edge-cases actually are diseases and the public are wrong in their common-sense interpretation (as Cooper (2002) does), but this cannot resolve problems where the same set of circumstances is sometimes called a 'disease' and sometimes not. For example, society greatly prizes 'height' as an attribute (especially for men) and

those with a deficiency of 'height' typically have poorer outcomes on a range of measures (Deaton & Arora, 2009). Take two otherwise identical short children and imagine that one has Growth Hormone Deficiency (a genetic condition causing them to be shorter than average) while the other has very short parents (a genetic condition causing them to be shorter than average). Both can be treated with Human Growth Hormone, a cheap and safe medicine that causes growth in children. While both are identically burdened by circumstances outside of their control, one has a disease and one does not (Buchanan, Brock, Daniels, & Wikler, 2001). Appealing to mixed accounts does not solve this except by appealing to social accounts so broad that they cease to function as a useful guide to resource allocation, which is the point of undertaking this definitional work in the first place.

One could take an even more radical line and argue that there is still a bullet to bite here and that the public are entirely mistaken in their understanding of what a disease is; perhaps *neither* child has a disease and disease should be entirely defined as strict insult to the biological systems. Szasz (1960) denies that mental diseases exist on the basis of this logic. These approaches are not available to us, however, as otherwise we are proposing the 'straightforward' solution to the problem of NHS Subversion actually involves radically redesigning the NHS around Szasz's rather controversial theories of disease. Overall, there is no reasonable way to define health such that the definition perfectly cleaves between health and non-health, or even only fails in artificial edge cases.

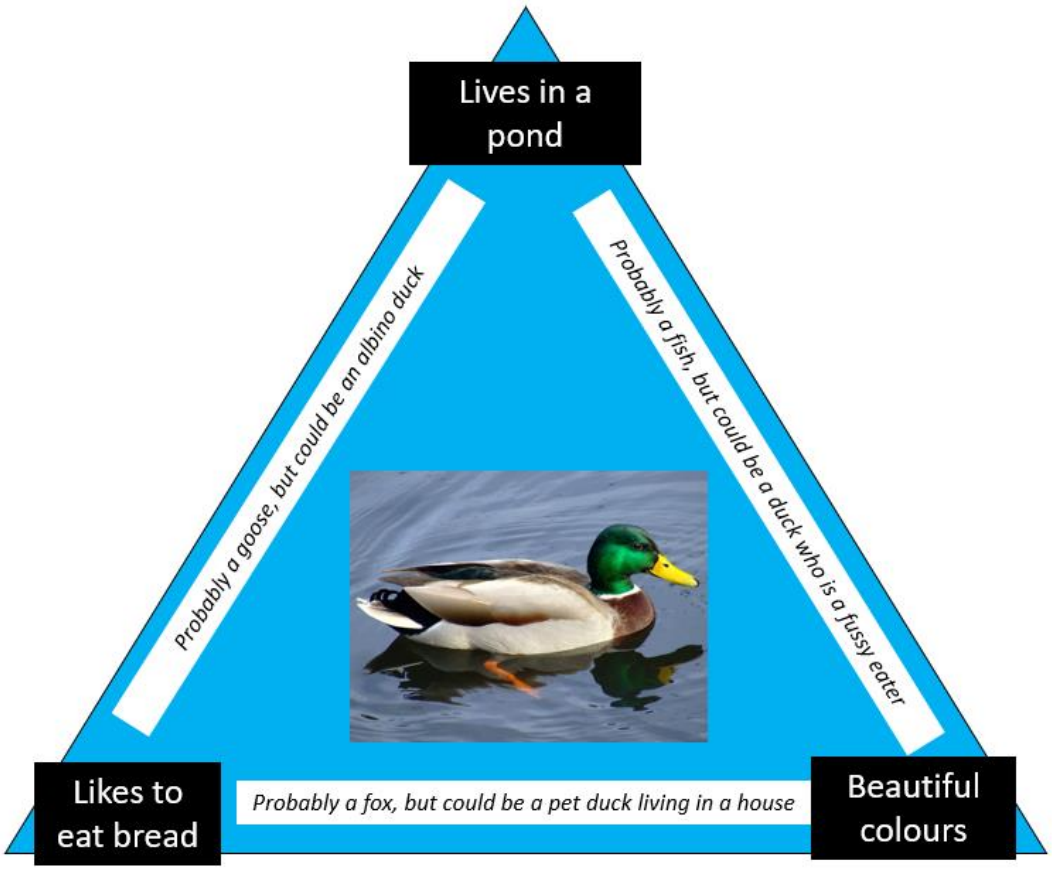
2.3.3.3. Health as homeostatic cluster property

As argued above, no theory of health is adequate to capture every way in which the NHS delivers what it would conceive of as 'health' – we see from Table 1 that each definition excludes at least one token example of the sort of thing that NHSes generally are concerned with. However, it is also clear that the vast majority of diseases are uncontroversially captured by all three definitions. This implies that diseases must have some regularities which mean we can distinguish them from non-disease – that is, it is unlikely that all NHSes have colluded to assemble a completely arbitrary collection of things to form the basis of their clinical interventions ('conventionalism') because we can delineate the majority of disease from non-disease by appealing to shared properties diseases have ('naturalism') (cf. Quine (1969)).

A natural kind does not necessarily need to be identified by a single feature that delineates it from non-members of that kind (Millikan, 1999), which is valuable as it appears no single definition can completely identify what the NHS understands health to be. If a collection of features are jointly but not individually constitutive of a natural kind then we describe that kind as possessing a 'cluster property' (Boyd, 1991). Some important thinkers are somewhat equivocal on whether the cluster property of natural kinds itself should be a natural kind (i.e. that there is some natural reason for properties to cluster) – for example, Quine seems to indicate that any set of objects which share some natural property (such as 'the set of all white objects' or 'the set of all positively charged objects') might be considered a natural kind (Quine, 1969), but more commonly it is required that there is some underlying reason for members of a cluster property to preserve their shared properties (Boyd, 1991) – that is, that the cluster property is 'homeostatic' (Boyd, 1991).

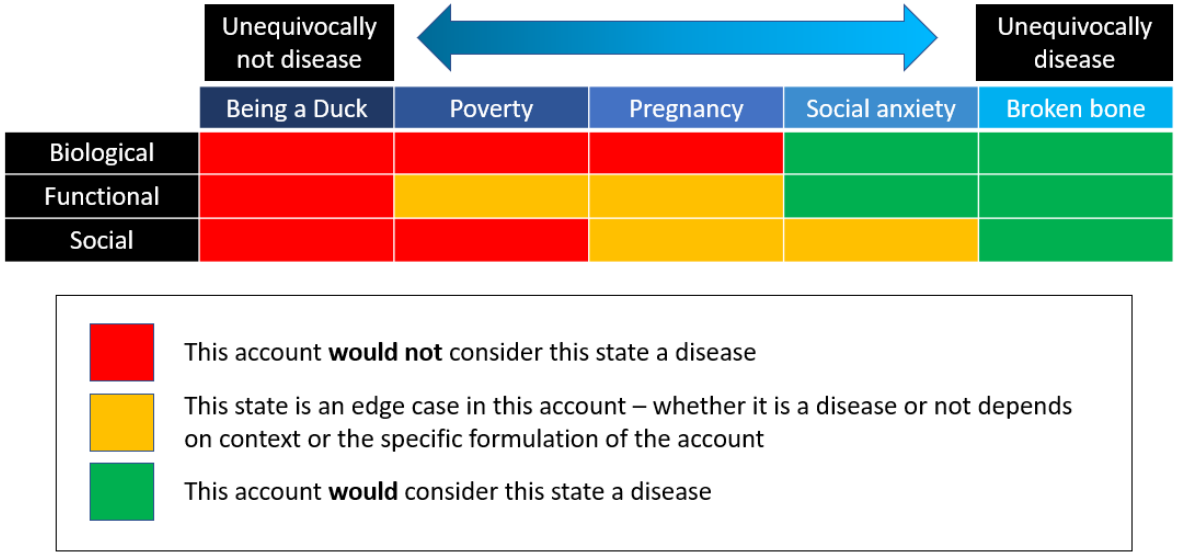
To illustrate this, Boyd suggests that biological species are a paradigmatic example of a homeostatic cluster property; for example, ducks mostly live in ponds, eat bread and have beautiful colouration – any animal we saw with those three properties would be very likely to be a duck. However, we could not rule out spotting ducks who do not have one of those properties (as in Figure 4) and indeed it is possible if unlikely to see a duck with none of these properties – we would presumably recognise them as ducks by appealing to a larger pool of properties that delimit a duck from a non-duck (such as quacking or being less than a foot high and so on). These qualities are homeostatic because evolutionary pressures select against ducks who live in deserts, who are fussy eaters or who have drab plumage and so cannot attract mates. There is at least one sense in which animal species are arbitrarily constructed (i.e. because we might choose to group animals by colour or friendliness rather than the ability to exchange genes) but it is possible to find other examples to illustrate the concept, for example the chemical elements in the periodic table (Rubin, 2008).

Figure 4 – Schematic representation of a homeostatic cluster property of ducks, with the central example of a duck at the centre and less central examples of ducks around the perimeter



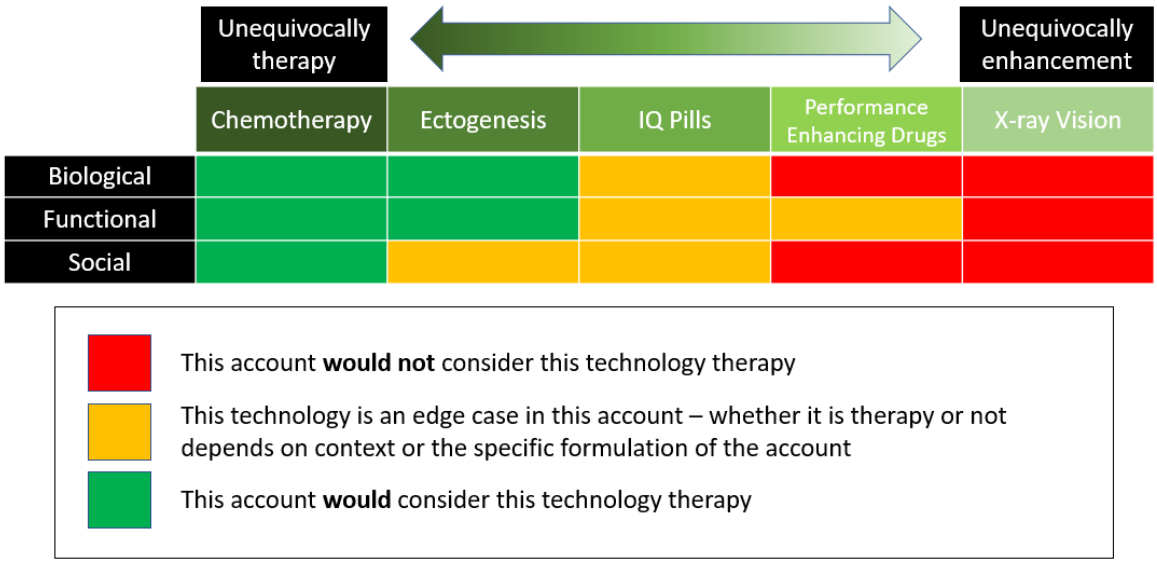
There is a limited but informative literature making the connection between the definition of health and the metaphysical literature on natural kinds (Kendler, Zachar, & Craver, 2011). Reminding ourselves of Cooper's impressive but flawed 'mixed' definition: diseases should be bad, unlucky and potentially treatable. We might consider each of these to be a cluster property of the disease kind, with most diseases very centrally being bad, unlucky and treatable (for example broken bones), some diseases missing one of these three criteria (for example sickle cell anaemia, obesity, social anxiety disorder) and perhaps even a very rare token disease which debatably fails all three criteria (for example, unwanted pregnancy or sociopathy in a society that rewards violent and promiscuous behaviour as per Mealey (1995)). This concept is schematically illustrated in see Figure 5.

Figure 5 – Representation of how states might be classified as more or less disease-like, given the centrality of their disease-ness on the three definitions of health



If 'health' is a cluster property then this means that 'therapy' – the thing we do to people to give them more health – cannot have a consistent and coherent target in every case (that is, for the possible set of interventions we can undertake on a patient, we cannot say for sure whether they will affect that patient's health even if we have perfect knowledge of whether it will affect their well-being in general, such as a perfect treatment for social anxiety). Figure 6 demonstrates how three example technologies – ectogenesis (artificial wombs), pills which enhance intelligence and physical / creativity performance enhancing drugs – might be classified as either therapy or enhancement according to the account of disease used to arrive at the given definition of therapy.

Figure 6 – Representation of how states might be classified as more or less therapy-like, given the centrality of their therapy-ness on the three definitions of health



This therefore means that the 'bioethicists' response' to the problem of Subversion fails; we cannot distinguish therapy from enhancement in all cases, and therefore cannot guarantee that the NHS has a consistent response to enhancements by just banning them.

2.4. Working definitions of human enhancement

2.4.1. Introduction

In Section 2.3, I argue that the two strongest arguments against the NHS Subversion model – one relying on a health economics literature and one on a bioethics literature – fail to adequately address the problem of NHS Subversion. This therefore indicates that the remaining work in this thesis is non-trivial, and may produce results of value to the NHS. In order to progress this remaining work, it is necessary to define 'health-related human enhancement', the central topic of this thesis.

Although it is easy to specify roughly what is meant by 'enhancement', actually generating useful philosophical work out of the concept is challenging (Menuz et al., 2013). In fact, as we know from the discussion in Section 2.3.3 that there is no clear boundary between therapy and enhancement, we know that it will be impossible to find a definition of 'enhancement' which satisfied all possible use-cases of the word (if this were not true then we could simply define 'therapy' as all that which is not 'enhancement' and solve the problem from this end).

Nevertheless, it is critically important to create at least a working definition of what an 'enhancement' is, in order to make it possible to search the literature for that concept, or implement that concept into

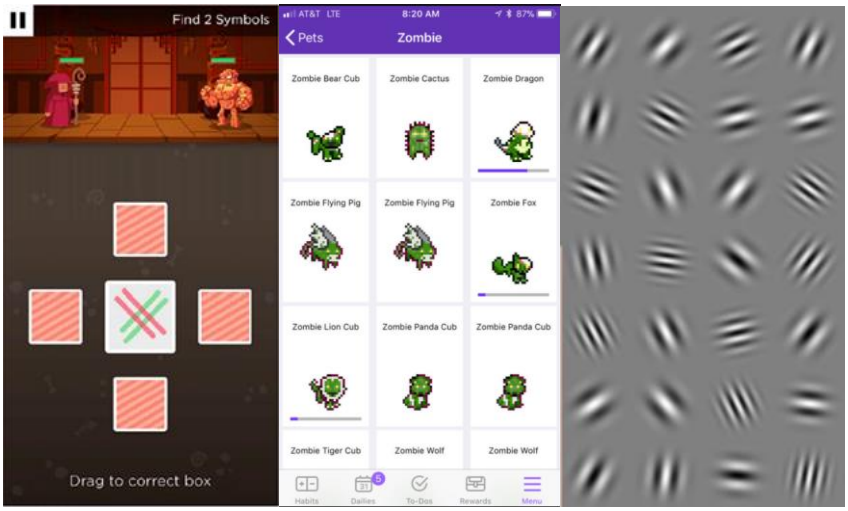
a health economic model. It should be noted therefore that the process here is 'ameliorative' rather than 'descriptive' (Haslanger, 2006). That is to say, whereas in Section 2.3.3 we were looking for a definition of 'disease' that fit with how the term was actually used by NHSes ('descriptive'), since enhancements don't actually exist yet it is much easier to bite bullets and therefore make the definition as useful as possible to future health economists working in this area ('ameliorative' – how we *should* use the term). Furthermore, part of the process must be to distinguish the set of health-related enhancements from the set of enhancements more generally, such as those used to enhance performance at sports (Schermer, 2008).

2.4.2. What is enhancement?

2.4.2.1. Example of enhancements

The most fundamental feature of human enhancement technologies is that they represent a recognition that modern technology offers the opportunity to modify basic parameters of the human condition, which were previously thought immutable (Bostrom & Roache, 2008). Many authors focus extensively on the methods by which that modification might be delivered – be it "nanotechnology, biotechnology, information technology and cognitive science" interventions (Menuz et al., 2013) or "genetic engineering, pharmacology, bioengineering, cybernetics and nanotechnology" interventions (Brey, 2009), but for a working definition it is reasonable to be fairly substrate agnostic – the *method of delivery* does not define an enhancement, but rather the capacity to alter the human condition in important ways. For example, Figure 7 illustrates a number of 'computer-aided' enhancement techniques where the enhancement is not even conceptually similar to existing healthcare interventions; from left to right it shows details from the game *Wizard* which purports to train episodic memory, the game *Habitica* which purports to reduce procrastination, and the game *Extreme Eye Exam* which purports to improves visual acuity (Sahakian et al., 2015).

Figure 7 – Computer-aided techniques for human enhancement



The literature is almost unanimous that our ability to 'modify basic parameters of the human condition' may allow for health-related enhancements in domains which are not currently the domain of medicine – for example enhancing morality (Persson & Savulescu, 2019), deepening or creating love between individuals (Ferraro, 2015) or radically altering our concept of 'personhood' (Lawrence, 2017). This does not necessarily mean that enhancements generally (or even examples of those enhancements in particular) are outside the domain of health forever – there are many examples of aspects of the human condition which were at one point not considered to be health-related being later recognised as health-related – for example control of fertility or psychological conditions.

Table 2 gives some examples of interventions which the NHS could theoretically undertake, and suggests a category they might belong to, by way of illustration of the concept of enhancement prior to a more rigorous definition.

Table 2 – Some examples of enhancement and non-enhancement in different contexts

	Not enhancement	**Enhancement**
Health-related	• Chemotherapy • Near future healthcare technologies like chimeric antigen receptor T cells • Non-NHS health technology like eating healthily and taking regular exercise	• Existing technology like vaccines, fertility control technologies like IVF and contraceptives, • Near-future technologies like bionic limbs / organs, 'Ectogenesis', cognitive enhancement • Far future technologies like radical life extension

Not health-related	• Taking a major promotion at work in order to have more money • Getting better at the videogame *Call of Duty* by playing lots of *Call of Duty* • Taking any substance whatsoever to improve performance at Chess or Bridge, on the grounds that relevant governing authorities don't believe the skill of bridge is 'enhanceable' in principle (Solomon, Noll, & Mordkoff, 2009)	• Bands taking hallucinogenic drugs to improve creativity or sprinters taking erythropoietin to sprint faster • Couples dosing on oxytocin (or similar) in order to deepen bonds of love between them (Ferraro, 2015) • Humans being modified to allow them to hibernate in order to permit interstellar travel (Szocik, 2020)

2.4.2.2. Enhancements and policy

The possibility of radically altering the human condition has led to a significant debate within the bioethics literature between those who take a relatively permissive view towards human enhancement ("bioliberals") and those who oppose it ("bioconservatives") (Roache & Savulescu, 2016). Briefly, there are many reasons why bioconservatives oppose human enhancement, perhaps the most prominent of which is that science is rapidly moving beyond areas where bioethicists have had enough time to think through the implications on the human condition; Sandel (2012) describes this as a kind of 'moral vertigo'. However, bioconservatives typically do not oppose the medical use of new technology (Greely, 2005), or oppose only specific kinds of technology in specific settings (Habermas, 2014). Many bioconservatives would even take a more radical line that there is something important or dignified about using technology to fight disease, and it should be viewed as morally good rather than merely morally permissible (Sandel, 2012). Section 2.3.3 argues that – at least with respect to a health economic theory of human enhancement – it is very difficult to support a therapy / enhancement distinction required of the first proposition. This therefore positions this thesis as fitting very closely to the 'bioliberal' position.

Important to note is that the existing literature on policy response is in agreement that our current ability to enhance humans is relatively minimal and heavily domain-circumscribed. For example, Bostrom and Sandberg (2009) records that memory enhancement techniques can improve digit recall

from 7 digits to 79 digits over time (Ericcson, Chase, & Faloon, 1980)). However, achievements attributable to enhancements are more than trivial - Paralympic athletes regularly post faster times than able-bodied athletes over long-distance track events, since their bioprotheses are more mechanically efficient than the human leg (especially when their equipment includes wheelchairs, which are significantly more biomechanically efficient than running – see Grassi (2019)). Furthermore, the field is progressing rapidly (Helmchen, 2005); because the nature of enhancements is to alter previously immutable aspects of the human condition, many authors suggest there is a possibility of a 'hard enhancement takeoff' due to cognitive enhancement – a human with an ability to field a higher cognitive load may design superior cognitive enhancements which may allow them to field a higher cognitive load still and so on (Sparrow, 2015).

Therefore, a working definition of enhancement relevant to this investigation does not need to predict exactly how the policy debates between bio-conservatives and bioliberals will resolve, but does need to be flexible enough to account for the fact that our understanding of the nature and role of enhancements in society may be radically different once this debate is more advanced.

2.4.2.3. Possible definitions of enhancement

Let us consider the following provisional definition, taken from the President's Council on Bioethics (President's Council on Bioethics, 2011):

Enhancement *… is the directed use of biotechnical power to alter, by direct intervention, not disease processes but the 'normal' workings of the human body and psyche, to augment or improve their native capacities and performances.*

As with the WHO definition of health (World Health Organisation, 1948), this is an extremely forward-looking definition for the time it was written, but is unfortunately not quite adequate for a theory of the health economics of health-related human enhancement – notwithstanding that it implicitly makes the same kind of claim about enhancement modality as e.g. Menuz et al. (2013) and Brey (2009) that enhancements must be 'biotechnical' to count, it also relies on a pre-existing concept of 'normal' workings of the human body, which has been broadly rejected by modern bioethicists as conceptually flawed (see Appendix A.2.1 for a detailed discussion on this point).

One could potentially improve this definition by replacing the concept of 'normalness' with a more precise idea of how enhancements might interact with health. For example, one might consider enhancement as taking an individual closer to their 'personal optimum state', taking into account physical limitations, social norms and personal preferences (Menuz et al., 2013). This probably does improve over the straightforward definition given by the President's Council on Bioethics, but risks health-related enhancement becoming indistinguishable from the concept of improving well-being generally, an approach which has also been rejected by theorists of health (Richman, 2004).

This criticism can potentially also be overcome, since we require the enhancements to be 'health related' for reasons unrelated to the matter of this definition (specifically, we require this because the context of the subsequent modelling will be various NHSes concerned only with health). Therefore it is possible to combine a definition of 'enhancement' like that above with a definition of 'health related such as that given by Tengland (2015):

Health related *means "… when the substance, or aid, increases ability or well-being, is integrated into the body, and does not harm the individual's fundamental health"*

This definition is not quite perfect, since – for example - it is clear that some enhancements might harm health a little in the process of improving some other capacity (e.g. coffee is a mild diuretic and an excellent stimulant, so many people drink it to perk up in the morning despite the diuretic effects). It also rules out the use of computer assisted enhancements which are not integrated into the body such as those illustrated by Figure 7. However, looking at the broad literature on enhancements it catches most of the fundamental methods and outcomes of the enhancement debate, making it suitable for this research project with some modifications.

Therefore, as a working definition for the purpose of this project we can combine the straightforward insights of the President's Council on Bioethics and patch weaknesses with reference to further work by Menuz et al. (2013) and Tengland (2015):

For the purposes of the upcoming literature review and modelling, ***health-related human enhancement*** *is the directed use of an intervention to augment or improve a human's native*

capacities and performances such that the result is closer to the 'personal optimum state', without deliberate harm to that individual's fundamental health, or deliberate augmentation of non-health capacities.

It is entirely understood that this definition cannot possibly be the final word on the subject; notwithstanding it is already concluded that there is no possible single definition for a homeostatic cluster property like 'health' (Rubin, 2008), there are concepts contained in this definition which would cause very serious philosophical problems if unpacked. For example, the notion that non-health capacities cannot be deliberately enhanced as part of a health-related enhancement is almost a restatement of the principle of 'double effect' which is generally considered inconsistent with a consequentialist moral standpoint and therefore potentially meaningless in the health economic paradigm adopted in this thesis (McIntyre, 2004). Broadly, however, the definition is serviceable for the purposes of reviewing the literature and creating economic models. More important than trying to directly define a term which we know will elude direct definition is understanding the limitations that this definition brings, and therefore what sort of enhancements might fall through cracks in the definition.

2.4.3. Possible failure cases of this definition

2.4.3.1. Almost anything could be an enhancement, leading to definitions which are so permissive they are useless

Viewed in a certain light, almost anything could be construed as an 'enhancement'. Greely (2005) gives the examples of stone tools, control over fire and wearing clothing made from animal pelts as examples of 'enhancements' that helped early humanoids come to be so dominant in the modern day. At some point we must draw a line between things that are enhancement and things that are not, lest the concept of health-related human enhancement become indistinguishable from the concept of technology more generally (Bostrom & Roache, 2008). This failure state is not so severe in the context of this thesis, since 'obviously non-medical' enhancements like stone tools and control over fire are not the same sorts of enhancements which will cause NHS Subversion. However, there may still be edge cases where a problem is presented – for example 'wireheading' is a hypothetical enhancement where an electrical current is applied directly to the pleasure centres of the brain

(Turchin, 2018) which is a central example of a 'health related human enhancement' according to the above definition but would probably not really be considered to be a meaningful enhancement of one's own life when viewed more holistically (Turchin, 2018).

2.4.3.1. Some radical interventions which meet almost every criterion for enhancement don't fit comfortably into the standard use of the term

Section 2.3.3 describes problems with separating enhancement from therapy, but there may exist other kinds of non-enhancement that are difficult to separate from enhancement. For example, a medical intervention which allowed a person to breathe the highly toxic atmosphere on Venus appears to enhance them in some sense (the sense of bringing the person minutely closer to their own 'personal optimum state' which for most people will include 'not dying on Venus') but also fail to enhance them in any relevant sense that person would care about (since people cannot generally travel to Venus and there is nothing much to do there anyway (de Melo-Martín, 2010)). Menuz et al. (2013) call these traits 'overcapacities', and they are distinguished from enhancements in that they do not assist with human flourishing (de Melo-Martín, 2010). This is perfectly sensible analysis, but does not fit easily in a framework where our definition is explicitly written to avoid talk of 'flourishing' in a general sense.

Another problem along these lines is that it is possible to modify but not enhance the human condition, which we could refer to as 'biomodification'. For example, Sacks (2012) describes a patient who loses the ability to see in colour, such that they can only see in shades of black and white. The patient does not want to be 'cured', since they have begun to organise the world around them in terms of "subtle textures and patterns" which are obscured when viewed in full colour. The patient would argue that monochrome vision is a 'biomodification' rather than an 'enhancement' of the human condition, in the sense that it offers a different perspective on the world which is equally valid to a colour-viewing perspective. Other examples which could maybe be considered along the same lines are tattoos, piercings and perhaps even circumcision (Savulescu, 2013) in the sense that they allow for individual self-expression without any specific effect on the person the procedure is done to except those effects which society bestows on an individual. Biomodification presents no problem for the NHS when the modification affects only self-expression (as in the case of tattoos), but in some

cases the ability to self-express is directly constitutive of health. For example, it is implausible to regard sex reassignment as an enhancement, since on average no trait is improved beyond baseline (Bracanović, 2017), and therefore the claim must be – as most people would agree with – that there is something inherently important to one's health of living as the gender one self-expresses as.

Finally, it is possible to radically modify the body in a way that harms it, or situationally harms it, which we could refer to as 'de-enhancement'. Menuz et al. (2013) give the hypothetical example of a pilot who modifies their vision to make themselves extremely longsighted, giving them a significant professional advantage but reducing their ability to participate in recreational activities like reading. Other actual or potential de-enhancements discussed in the literature are removing painful or embarrassing memories (Tännsjö, 2009), genetically engineering a deaf child (Harvey, 2004) or removing a limb to treat body integrity identity disorder (Ryan, 2009). An interesting perspective on this final example is the case of 'DB', an 11-year old girl described in Menuz et al. (2013). DB was born with a congenital deformity of the right leg meaning that she could not articulate it but the tissue was otherwise healthy (that is, DB had no risk of necrosis or issues with pain, and was able to move around relatively easily with the use of a cane). DB requested that this healthy but non-functional leg be amputated in order that she could compete in the Paralympic Games. In some sense this is the opposite of the 'overcapacity' problem described above; DB's natural endowment was above the level she believed would allow for the greatest flourishing, and so – paradoxically – was able to 'enhance' herself by removing a capacity.

In the context of this thesis, these failure states should not alter any significant conclusions; they are all examples of labelling a non-enhancement as a kind of enhancement because of an over-permissive definition. The result – at worst – will be that it is harder than it needs to be to find a consistent NHS response to the problem of enhancements (if one exists) as the economic model may erroneously identify solutions which only work in the context of irrelevant enhancements, biomodification or de-enhancements.

2.4.3.2. To 'enhance' logically requires a baseline standard against which improvement can be measured, but this can't always be assumed to exist

To 'enhance' something requires that there be some baseline reference state from which we can judge whether something has been made better or worse (Menuz et al., 2013). There are some enhancements where finding a baseline state might be reasonably straightforward – for example it seems that more intelligence is always preferable to less intelligence (Hartog & Oosterbeek, 1998). For other enhancements such as facial attractiveness we could appeal to some statistical concept of 'normality' since there are many varying concepts of what facial attractiveness might be even if there is near universal agreement it is better to be attractive than not. But there may be a fundamental problem with classes of enhancement where there is no consensus on what represents the good life. For example, consider an intervention which causes you to love your partner more deeply might be prescribed to couples undergoing marital trouble (Enck & Ford, 2015). Some might believe that such an intervention is justified as a mere extension of the general duty to try and uphold vows of marriage where possible, others might believe that such an intervention removes an important element of human autonomy. Giubilini (2015) argues that there is no meaningful reference standard for this case, and that therefore either 'enhancement' cannot be defined (or a third category of 'value-free enhancement' must be proposed). This issue becomes even more intractable when considering perspectives outside the Western medico-philosophic framework. For example, Asian perspectives on the therapy / enhancement distinction are notably different from Western perspectives in a number of areas (Ida, 2010), religious Jewish perspectives on genetic engineering differ from secular perspectives on the same topic (Wolff, 2001) and so on.

The role of vaccines and preventative medicine present a significant challenge to this view; vaccines can be seen – depending on perspective – as 'enhancements' of the immune system (Erler, 2017). Indeed, some bioliberal authors note that the 'normal working of the human body' includes the desire to improve one's own lot in life, and therefore even extremely radical interventions such as flight or x-ray vision could be understood as being something other than 'enhancement' (Menuz et al., 2013).

This failure case seems fundamental – 'value free enhancements' are almost completely invisible to an economic model, since valuation of health states are supplied by society rather than by some

objective criteria in conventional health economic analysis (Dolan, Gudex, Kind, & Williams, 1996). Consequently, we cannot simply take some arbitrary set of characteristics as 'baseline' for the sake of having a reference point to define 'enhancement' against; the concept of value-free enhancements says that society might overall value an enhancement as being net neutral, even though some individuals in society might value it very highly while others have a strong negative valuation of it.

2.5. Conclusions

Unlike many problems in health policy, the problem of NHS Subversion could – in principle – be costlessly ignored under certain conditions. It is conditional on technological advances producing 'better than perfect' health at cost-effective prices; the technology might not be invented, or it might not be commercially viable to sell into regulated markets such as public health care systems at prices that make it more cost-effective than traditional medical advances, and if these technological advances never happen then the NHS never becomes Subverted.

However, this would not absolve policy makers from thinking about the regulation of such entities in advance, as by the time they are invented it will be, in a sense, too late to worry about them. Under these circumstances, it appears there are two possible solutions to the problem. The first is to deny that 'better than perfect' health is a meaningful concept with which to make decisions in a resource-constrained framework (the economic response) and the second is to deny that there is any difficulty identifying and refusing to fund Subverting enhancement medicines (the bioethics response).

The economic response proposes that there is no meaningful way of describing 'better than perfect health' in a health economic framework, since 'perfect health' is defined as 1 QALY per year and anything greater than 1 QALY per year is therefore mathematically undefined. The case for this position rests on the concept of 'anchor states' being fundamentally important to health economic analysis, whereas the response to this case demonstrates that health economists have broadly accepted the notion of 'worse than death' states and that health economic theory does not rule out moving the upper anchor either. Therefore, it is concluded that 'better than perfect health' is a meaningful concept, and health economic assessment of these states can proceed as normal.

The bioethics response proposes that it is possible to prevent NHS Subversion in at least one straightforward way, which is by banning the use of public money to fund enhancements (which will inherently prevent the funding of Subverting enhancements). In some ways this response is more straightforward than a the technical health economics response, since it is mostly in line with public opinion of enhancement funding (Heinz et al., 2014). However, this response rests heavily on the idea that it is possible to distinguish between therapy and enhancement all of the time – a single Subverting edge case would be all it would take to cause serious problems for the account. In general, the case for a therapy / enhancement distinction is not made satisfactorily (at least in the context of a health economic account of therapy and enhancement) and so there is no definition of health which captures everything that we would describe as a disease and nothing that we would describe as a non-disease, and every account of health fails on quite a central example of one of these two categories (see Appendix A.2 for further detail). In order to get at a genuinely useful concept of health we need to rely on fuzzier concepts such as all diseases sharing some sort of (potentially natural, potentially homeostatic) cluster property, which unequivocally rules out the possibility of a clear therapy / enhancement distinction, and thus rules out the bioethics response.

It should also be added that both of these responses try to prevent the NHS by being Subverted by a 'better than perfect' health enhancement. It seems equally coherent to imagine that life extension enhancements that do not improve quality of life to supernatural levels might also function as a utility monster (i.e. modifying the 'life years' element of the QALY), and that therefore Subversion could potentially occur even if one or both of the health economics / bioethics response was actually true. This observation could in principle be resolved if life years lived beyond the natural lifespan were inherently less valuable to an individual (maybe because you begin to see and accomplish everything you want to do and begin to run out of new challenges – see Pijnenburg and Leget (2007), Williams (1973), although if this is not actually the case then the existence of antigerontic enhancements fatally undermine the two responses considered in this Chapter. Since the impact of radical life extension on human quality of life is not known and since a working definition of enhancement is required anyway for later Chapters, it is assumed that life extension is outside the scope of the investigation.

Given that we are confident no clear distinction between therapy and enhancement exists, it is naturally impossible to create an unambiguous definition of enhancement for use in later Chapters. Nevertheless, after reviewing the literature on such definition and considering the edge cases which are ruled in and out by the selected definition, it is reasonable to conclude that a working definition of human enhancement can indeed be created, suitable for use as a basis of a health economic framework of ‘better than perfect health’. This in turn implies that there is a good chance that further investigation of the concept of NHS Subversion may cover interesting territory, and hence a Systematic Review of the Literature is indicated.

Chapter 3. Systematic review of human enhancement literature

3.1. Chapter summary

This Chapter assesses the literature on enhancement from a health economic perspective, using the technique of a systematic review to identify issues and perspectives on the topic of human enhancement in an HTA context.

The review takes the definition of 'enhancement' laid out in Chapter 2 to inform the review protocol (Appendix B.1), and the outputs of the review will be used to inform a health economic model of enhancement in Chapters 4 and 5.

The chapter begins with some notes on the unusual requirements and results of the review (Section 3.2 and Section 3.4 respectively). A discussion of the results and concluding remarks on the implications for subsequent chapters of the thesis is offered in Section 3.5.

3.2. Introduction

3.2.1. The importance of systematic reviews of ethical literature

A systemic review is an overview of primary studies which is conducted according to an explicit and reproducible methodology (Greenhalgh, 1997). Wormald and Evans (2018) describe the process as being like a piece of observational research conducted on a database. The advantages of conducting a review of the literature in a transparent and reproducible way are manifold, but the most relevant here are that it allows the reader to assimilate a large amount of information quickly, and to trust that that information will have bias explicitly limited by the techniques of the systematic review (Greenhalgh, 1997). Perhaps most importantly, systematic reviews have a 'corrective effect' on biased knowledge (McCullough, Coverdale, & Chervenak, 2007) and allow people to rapidly update incorrect assumptions about the state of the evidence without themselves having to read every paper published on a topic – leaving more time for original research. This could be especially important where information from multiple disciplines is being synthesised; readers without subject-specific knowledge of an area can rely on an unbiased review to help inform them of the state of thinking in the field.

In recent years, there has been interest in developing and extending the principles of systematic review to cover argument-based or normative ethical questions (McCullough et al., 2007) – that is, what Hunink et al. (2014) identifies as 'values' of the clinician, patient and healthcare system. Publications of systematic review of ethical thought are increasing year on year (Mertz, Kahrass, & Strech, 2016). The purpose of academic ethical discussion is – at least in part – to influence the behaviour of clinicians (McCullough et al., 2007) and so the question of how to present the current state of a particular discourse in a way which is unbiased, timely and easily accessible to clinicians is an important one. This review focusses mainly on an audience of policy-makers (especially health technology assessment agencies) but the insight is the same; presenting academic ethical discussion in a way which influences the behaviour of policy-makers is an important reason to consider reviewing this literature systematically.

There exists only one prior review into human enhancement in a resource allocation context (Wolbring et al., 2013). It had a broad focus (the entire health domain) and a non-systematic approach, but still only found one publication clearly and obviously linking resource allocation and HTA (Wolbring, 2005). The challenge addressed below, therefore, is the twin difficulty of identifying as much relevant literature as possible in a field where it is known literature will be hard to find, and ensuring that the method of extracting and synthesising this literature will be acceptable to a health technology assessment audience more used to conventional systematic reviews.

3.2.2. Methodological challenges with systematic review of normative literature

For the reasons described in Section 3.2.1 a systematic review is considered vital to bridge the gap between normative literature on human enhancement and the expectations of health technology assessment agencies who are the intended audience for the output of the review. Systematic review methodologies of empirical clinical literature are well established (Petticrew & Roberts, 2006), and therefore an obvious initial approach might be to apply conventional methods of literature review to this unconventional problem. This obvious approach would not be appropriate in this case, and may be inappropriate for *any* review of normative literature (Sofaer & Strech, 2012). This is because there

are a number of features of the bioethics literature that subvert assumptions of a 'traditional' literature review. For example:

- There may be no single standard for assessing the 'quality' of a paper in clinical ethics. In clinical medicine, the 'quality' of the paper is – relatively – simple to assess (Balshem et al., 2011), but this is not really a requirement of normative clinical ethics. For example, a key argument in a paper might be hypothetical, or counterfactual, or rest on the truth of premises which cannot be proved (Sofaer & Strech, 2012). Therefore, analysis of any one part of a normative publication could hinge on understanding the publication in its totality.
- Ethical literature in general, and clinical ethics in particular, is extremely 'dialogic' in its construction, meaning that arguments will often be direct responses to arguments made in the past. In the field of health economics and bioethics a classic 'dialogue' would be a claim that NICE unethically discriminates against the disabled (Harris, 2005), the response to that claim (Claxton & Culyer, 2006), the response to the response (Harris, 2006) and so on.
  Conventional systematic review would not straightforwardly handle a publication where part of the supporting argumentation was found in a different publication by a different author.

These challenges necessitate that before the review of the literature is undertaken, very serious consideration is given to available normative systematic review methodologies.

3.2.3. Review of methodologies

Two possible methodologies for systematic review of bioethics literature have been proposed – McCullough, Coverdale, and Chervenak (2004) and Strech and Sofaer (2012). McCullough et al. (2004) propose that standards very similar to a traditional systematic review are used, where the quality of each paper is assessed on a binary scale for each of five dimensions (with a 'half point' for partial fulfilment) and a table therefore presented to readers showing the papers reviewed, the position taken and the 'quality' of the paper recorded. They offer an example of this technique applied to the literature on concealed medicines (McCullough et al., 2007). By contrast, Strech and Sofaer (2012) propose a significantly more complex process where arguments rather than papers are assessed. They offer an example of the technique applied to post-trial access to trial drugs (Sofaer & Strech, 2011).

There are some examples of both techniques being used by authors other than those who invented the technique (Fleming, Frith, Luyben, & Ramsayer, 2018; Mahieu & Gastmans, 2012; Quaghebeur, Dierckx de Casterlé, & Gastmans, 2009), but in general there is no consensus on which is the best to use.

In addition, the search for review methodologies uncovered Scott et al. (2017), which argues that existing systematic review techniques are suitable for assessing ethical literature, providing quality assessment is carried out using an ethics-specific tool called the 'Q-SEA', but this is a relatively newer technique and there do not appear to be any examples of reviews employing it other than Scott et al. (2017) itself. In the absence of a worked example of this tool addressing the challenges raised in Section 3.2.2, it cannot be considered as a fully developed methodology and is not analysed further.

Table 3 below summarises these three approaches.

Table 3 – Summary information regarding methods of systematic review of normative ethical literature

	McCullough method	**Systematic Review of Reasons**	**Q-SEA Tool**
Key methodology paper	McCullough et al. (2004)	Strech and Sofaer (2012)	Scott et al. (2017)
Example of technique	Concealed medicines - McCullough et al. (2007)	Post-trial access to drugs - Sofaer and Strech (2011)	Autologous stem cell transplantation - Scott et al. (2017)
Focus of technique	Normative – What is the conclusion of the argument?	Empirical – What reasons have been given in support of the argument?	Process – Have unbiased techniques been used in the paper?
Quality assessment	Five-item yes/no checklist giving summary score	None	Ten item yes/no/partial checklist with no summary score
Analogy to existing techniques	Analogous to existing systematic review methods, but with changes in some places	Completely unique, and specific to reason-based argumentation	Exactly as per existing systematic review methods, but with alternative method of scoring ethical literature

3.2.4. Analysis of methodologies

The key strength of a McCullough review is that it is conceptually similar to a conventional Cochrane-style review where quality assessment is performed on a per-paper basis (McCullough et

al., 2007); this makes it highly suitable for a review which will be read by health policymakers. McDougall (2014) goes further, highlighting that the use of an Intervention/Comparison dyad in the review question makes it highly suitable for economic analysis, since that dyad inherently contains the idea of "a choice between alternatives" (McDougall, 2014), analogous to the concept of opportunity cost. It is unequivocally systematic in its approach – especially to quality assessment – which might grant it a particularly relevant status to clinical decisionmakers who don't have time to assess an entirely new review methodology when determining what ethical decisions to make (Strech, Synofzik, & Marckmann, 2008). However, this may also mean that it is limited in its ability to respond to unusual characteristics of ethical literature; for example, Quaghebeur et al. (2009) or Mahieu and Gastmans (2012) use a modified McCullough method because the structure of the method is inappropriate for their review, which undermines the benefit of systematisation.

However, Strech and Sofaer (2012) criticises this form of review, arguing that the McCullough review has several inadequacies which can be fixed by reviewing the reasons empirically observable in the paper rather than the normative ethical statements the empirical reasons correspond to. They prefer a Systematic Review of Reasons, where arguments are systematically extracted without the potential for a biased 'summing up' of an entire paper which could contain multiple arguments (Sofaer & Strech, 2012). This approach could potentially be more comprehensive, since it can account for all possible ethical positions discussed in a paper, and more transparent, since it does not force authors to make a subjective judgement on what a paper is trying to 'say'. The output is therefore potentially more suitable for future research, since the data extraction is not specific to one ethical question. Furthermore, in some areas the McCullough review may be outright misleading if the literature could support two internally consistent but mutually exclusive ideas and the reviewer sums this up as 'no consensus' (Sofaer & Strech, 2012).

The appropriate bioethics systematic review methodology depends heavily on context – especially the intended audience (Ives & Draper, 2009). Given that the intended audience of this review is health economists (or policymakers familiar with health economic concepts) the congruity of the 'McCullough method' with existing economic theory appears to overwhelmingly favour that

approach. A Review of Reasons requires a "particularly sophisticated critical lens" from the reader (McDougall, 2014) to avoid traps such as a merely counting the incidence of a certain type of reason (Strech & Sofaer, 2012). This is an unreasonable requirement when bridging two disciplines; we should not expect experts in one discipline to be experts in another. Therefore the 'McCullough method' is adopted for this review, with minor amendments made to include health economic specific outputs.

3.3. Review protocol

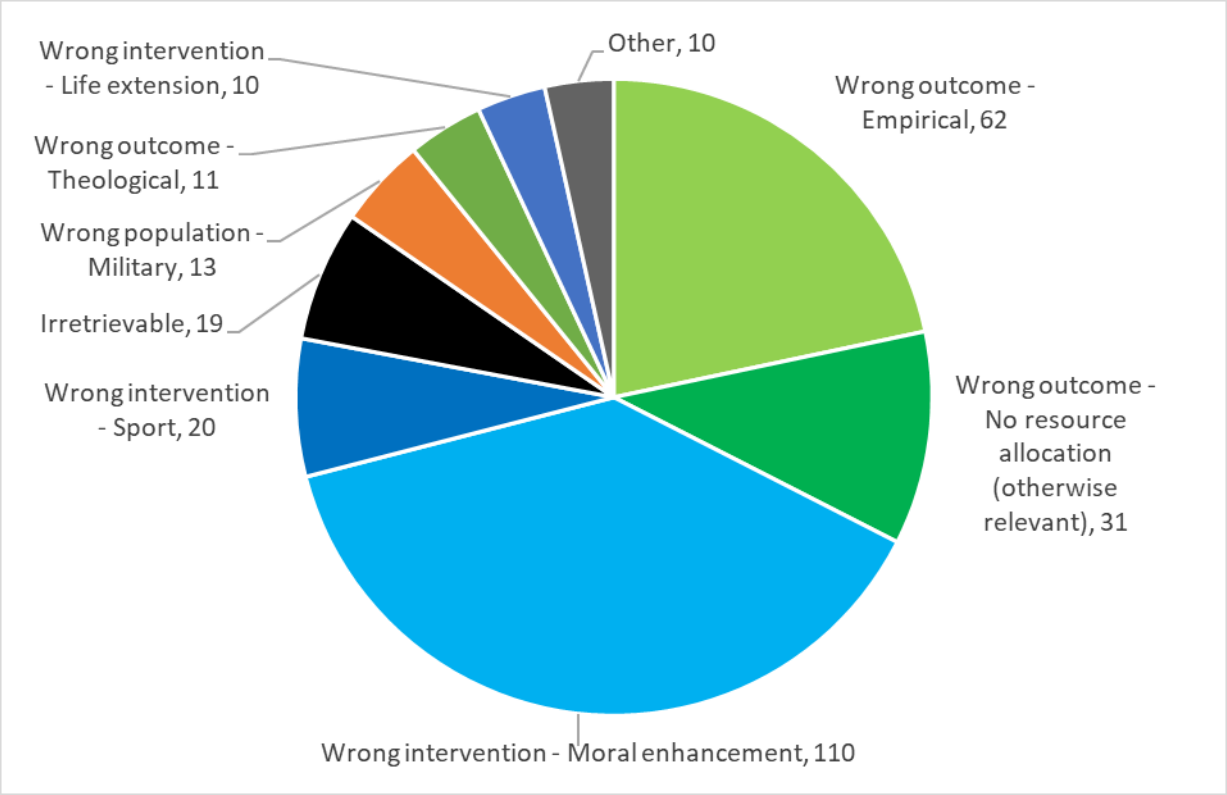
A systematic review using the 'McCullough method' was undertaken in March to April 2020 based on the review question "In publicly funded healthcare systems, is it ethical to treat human enhancement technologies as presenting only 'generic' issues of resource allocation?". As neither the general principles of systematic review nor the specific application of the 'McCullough method' to this type of evidence are novel to this work, the review protocol is described in Appendix B.1 as background information only, and not commented on further in the main body of the thesis.

3.4. Results

3.4.1. Overview

1876 titles and abstracts were included for screening (after deduplication and the removal of foreign-language publications). The vast majority of these titles and abstracts were excluded for reasons of irrelevancy (see Appendix B.3), but 286 were excluded for failing one or more inclusion criteria, most commonly that the enhancement being considered was not relevant to a publicly funded healthcare system.

Figure 8 – Excluded studies, grouped by reason for exclusion



Of the 79 publications included and assessed in full-text, 24 met all the inclusion criteria. For details of included studies see Appendix B.4, and for details of excluded studies see Appendix B.5. Quality of included studies was generally high (see Appendix B.4), although as expected none contained explicit health economic reasoning.

In general, five major areas of interest regarding resource allocation in a public payer healthcare system were identified in the literature and are summarised in Table 4. Note when stating that these areas were 'identified' this does not mean a procedure such as thematic analysis was undertaken to identify and categorise the groupings – this would not be consistent with the methodology described in Appendix B.1. The groupings are simply for ease of understanding where, approximately, publications focus their attention.

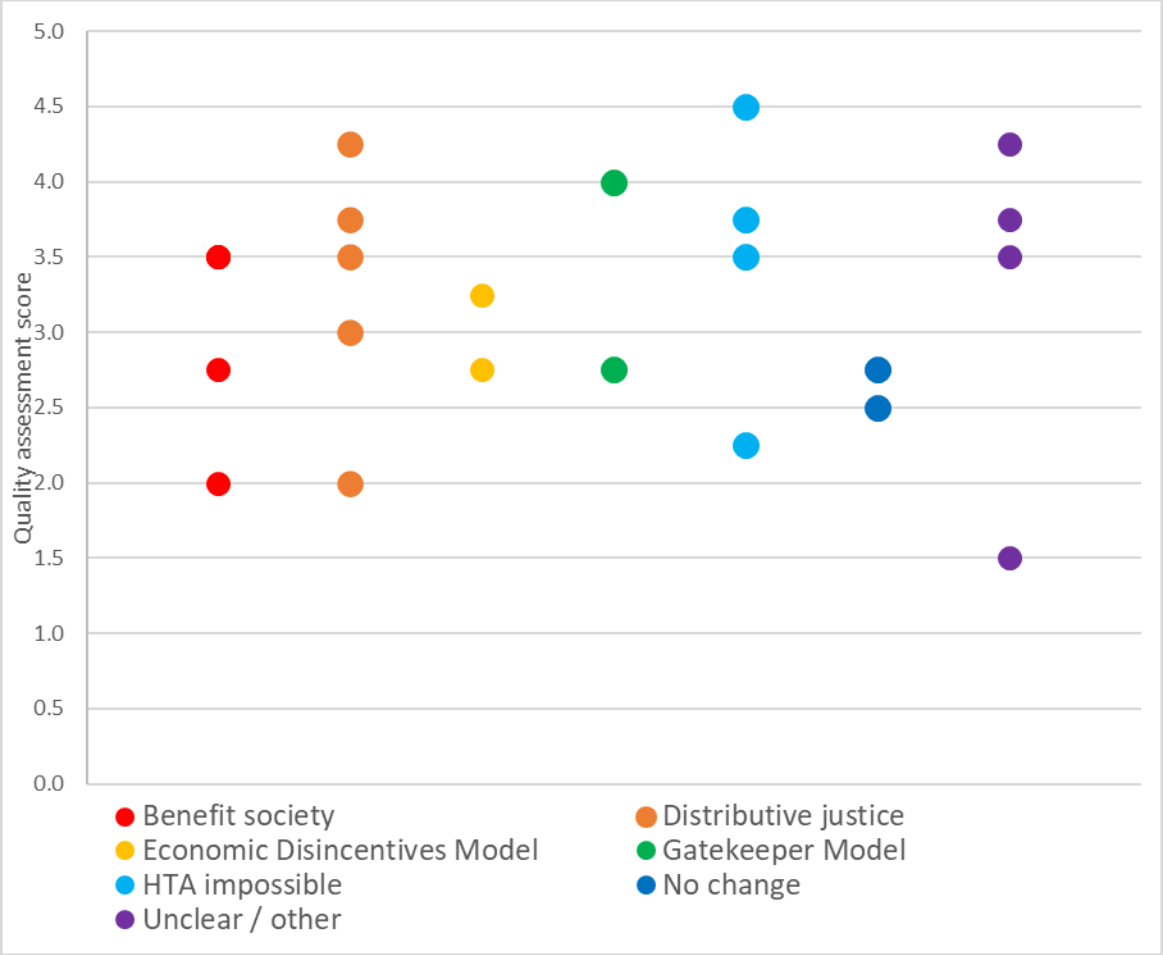
Table 4 – Results of literature review, grouped by broad models of technology assessment

Position	**Description**	**Associated publications**
Benefit society	A general observation that human enhancement has an unusual relationship with *whole society* costs and benefits	Buchanan (2008); Goodman (2010); Lamkin (2011); Outram and Racine (2011a); Savulescu, Ter Meulen, and Kahane (2011)

Distributive justice	A general observation that human enhancement is associated with inequalities relevant to HTA decision-making	Allen and Strand (2015); Kim, Hong, Kim, and Yoon (2019); Lavazza (2019); Lin and Allhoff (2008); Ray (2016)
Economic disincentives model	A specific model of regulation where consumers are licensed to use human enhancement technologies	Dubljevic (2012b); Dubljević (2015)
Gatekeeper model	A specific model of regulation where clinicians act as gatekeepers to human enhancement technologies	Danaher (2016); Enck and Ford (2015)
No change	HTA conducted according to recognised methods appropriate for human enhancement	Chan and Harris (2006); Maslen, Savulescu, Douglas, Levy, and Kadosh (2013)
"HTA impossible"	A variety of positions which if correct would mean that HTA as currently conducted would not be possible for human enhancement technologies	Dubljevic (2012a); Rajczi (2008); Shaw (2014); Sparrow (2015)

Comparing the position taken to the quality of the paper does not indicate that higher-quality papers are associated with any particular position (see Figure 9), and also demonstrates that the literature generally is of a medium to high quality. Furthermore, the literature was not evenly distributed around different methods of enhancement; moral and cognitive enhancement were highly overrepresented in the search outputs, with other forms of enhancement (especially cosmetic and physical) not considered to nearly the same degree. *Post hoc* searches of the literature for just these key terms suggested that these are genuine gaps in the literature rather than artefacts of an error in the search strategy or execution.

Figure 9 – Distribution of paper position versus paper quality assessment



Four publications (Bostrom & Sandberg, 2009; Dubljević, 2013a, 2013b; Franke, Northoff, & Hildt, 2015) did not take a specific relevant position themselves, but included discussion on a number of relevant positions and so are included in subsequent discussion but not in Table 4. Additionally some authors included discussion of different positions before reaching their preferred conclusion; for example Dubljević (2015) considers the Gatekeeper model as a counterpoint to his preferred Economic Disincentives model, and so these papers are relevant to both areas of discussion.

A final position is included in Table 4, which is that of "HTA impossible". This conceptually represents an argument that specific features of human enhancement technology mean that economic assessment in line with existing regulatory bodies' methodology is impossible. In that sense a resource allocation issue is presented because there are no existing methodologies capable of making resource allocation decisions on human enhancement technologies. In practice, no author makes this specific argument but rather each publication in the "HTA impossible" category makes a

philosophical argument which – if extended into the health economics domain – would present very major challenges to health economic assessment of a specific technology.

Further discussion of each position follows in the next two Sections. For convenience, the positions are grouped by whether, taken literally, the publication is consistent with current HTA methodologies (Section 3.4.2) or would reject current HTA methodologies (Section 3.4.3).

3.4.2. HTA may be possible

3.4.2.1. Benefit society

Many authors observe that human enhancement has the potential to benefit society as well as offer individual benefits. Savulescu et al. (2011) describe a comprehensive range of mechanisms that link enhancement to social benefits, ranging from a reduction in road traffic accidents to preventing the loss of house keys (an event with an alleged annual cost of £500m in the UK, according to Halifax Home Insurance (2005) cited in Savulescu et al. (2011)). Other authors make a similar point in more general terms; there may be such benefits to society of enhancement that cognitive enhancement should be treated as a public health necessity (Outram & Racine, 2011a) or subsidised by the government to promote its use (Buchanan, 2008).

Other authors make similar points but from a more bio-conservative perspective. Lamkin (2011) observes that there may be negative externalities from the enhanced incident onto the non-enhanced. Using the emotive example of cosmetic skin lightening, Lamkin observes that in general being light-skinned results in better outcomes than being dark-skinned, largely because of racial prejudice against dark-skinned people. Therefore, if a technology was available to convert dark to light skin, many dark-skinned people may want to use that technology to benefit from the better outcomes accruing to their light-skinned peers. But if only some dark-skinned people have access to the technology, then it is highly likely that prejudicial attitudes would harden towards the remaining dark-skinned individuals (potentially leading to a self-reinforcing spiral).

Goodman (2010) makes a similar but more general point that certain human activities are zero-sum (meaning that any gains by one participant are exactly and equally offset by losses to another participant – Goodman gives the example of a game of baseball). In a zero sum game the

enhancement of one participant is merely to the detriment of other participants, and hence society as a whole is made no better off by allowing enhancement in these situations. (However, Goodman also reasons that enhancement might be looked upon favourably in the case of collaborative endeavours such as the creation of a music album, and so takes the view that the circumstances are critical in deciding which enhancement benefits or harms society overall).

3.4.2.2. Distributive justice

Typically, publicly provided healthcare must find a compromise between efficiency (providing as many QALYs as possible) and equity (attempting to generate those QALYs fairly across society, however 'fairly' is defined) (Wagstaff, 1991). Insofar as concerns about efficiency are raised in Section 3.4.2.1, concerns about equity are raised by authors described in this section. In general, many authors both included and excluded from the review observe that enhancement has the potential to reinforce existing inequalities, but only Allen and Strand (2015); Kim et al. (2019); Lavazza (2019); Lin and Allhoff (2008) and Ray (2016) describe these inequalities in terms of a resource tradeoff.

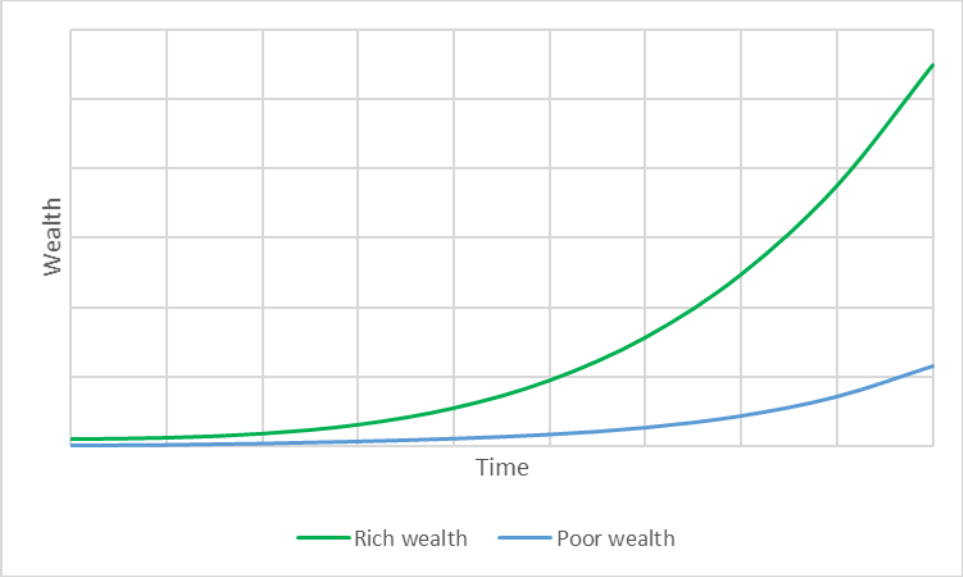
Lin and Allhoff (2008) describe the issues common to all publications in the 'distributive justice' grouping. They observe that the economy does not require everybody to be equal for that economy to be just, but that enhancement raises the possibility that the enhanced might be so effective that the unenhanced become "dinosaurs in a hypercompetitive world". They go on to note that access to enhancements in anything approximating a market system, even if 'fair' in principle, could be rendered unequal *ex post* by unequal starting positions (in particular, those who start with more resources are more likely to be able to pay for access to enhancement). Therefore, the conclusion of Lin and Allhoff (2008) – although not entirely clear – is that regulation is required to ensure the gap between enhanced and unenhanced remains at acceptable levels. This is broadly the conclusion of the US Bioethics Commission described in Allen and Strand (2015), arguing that equitable access to certain classes of enhancement is important.

Ray (2016) and Lavazza (2019) are more specific in their recommendations, offering outline models of resource allocation. Ray (2016) argues that the existence of enhancements allows society to treat 'socioeconomic status' as a domain of disability, and consequently use enhancements to correct this

unchosen disadvantage. Lavazza (2019) argues that it would be immoral to force people to take enhancements (as some authors in the 'Benefit society' grouping in Section 3.4.2.1 might propose), but that the resulting inequality should therefore be regarded as illegitimate. Consequently, society should compensate those who do not wish to use cognitive enhancement for the lessened economic opportunities available to them.

The threat of an 'inequality cascade' is described by Sparrow (2015) (and perhaps hinted at by Lin and Allhoff (2008)). The concern is that enhancements can be modelled as an investment in human capital (Shaw, 2014), and that therefore those able to access enhancements in the first period will be better positioned to access enhancements in the second period and so on. Figure 10 demonstrates the output of a simple model where two agents interact with an enhancement market. Both agents initially have the same value to the market, but can increase their economic productivity by investing a certain proportion of their wealth into enhancements (which, for the sake of argument, they always choose to do in this example). The agents differ initially only in that the 'rich' agent (green line) can afford an initial enhancement at time t=0 while the 'poor' agent (blue) cannot, so the rich agent benefits disproportionately. The output of the model demonstrates quite simply that although both rich and poor alike benefit from enhancement, the rich agent benefits enormously more than the poor agent. Insofar as any activity in this economy is zero-sum, the poor agent is in a noticeably worse position than they were at time t=0, and the inequality gap will keep expanding as time goes on. There do not appear to be any actionable proposals of how to prevent this 'inequality cascade'.

Figure 10 – Output of a simple model demonstrating the compounding effect of 'inequality cascade' given (relatively) trivial differences in starting endowment (far left of graph)



3.4.2.3. Economic disincentives model

The economic disincentives model (EDM) is the most conceptually complete model of resource allocation under a health economic perspective. The model is effectively the work of a single author across four papers (Dubljevic, 2012b; Dubljević, 2013a, 2013b, 2015). The concept of the model is described in detail in Dubljevic (2012b). Under the EDM, enhancements would be licensed by a regulatory authority for over-the-counter use (that is, analogous to the EMA or FDA licensing requirements that exist currently), but available for sale only to those individuals who pass an additional personal licensing procedure. This procedure would contain, for example education about the side-effects of the enhancement, an exam to demonstrate that consent for the enhancement was informed and proof of an insurance payment to indemnify the healthcare system against treating any side effects (with the intent of making the system self-financing). Dubljević (2013a) extends the model by suggesting that the licensing requirements could be used to cross-subsidise other areas of the healthcare system – for example by funding research into treatments for rare diseases.

A throwaway line in Dubljevic (2012b) explains that enhancement "would also be available via prescription", which would seem to indicate that they considered the EDM an adjunct to conventional health technology appraisal rather than a replacement, in which case the EDM does not add insight to the overall question of how to make decisions on resource allocation in a health economic context. However, Dubljević (2015) observes that this approach could not possibly work for tDCS

[transcranial direct current stimulation] devices and therefore there are at least some human enhancement technologies for which the EDM is explicitly intended as a solution for the problem of resource allocation.

3.4.2.4. Gatekeeper model

Gatekeeper models propose that some agency or individual acts as a 'gatekeeper' for human enhancement technologies. The 'gatekeeper' uses their judgement to ensure that only those who deserve access to some technology (based on some pre-agreed criteria) are able to receive it. A number of publications consider this model, with most indicating that the gatekeeper be either a specially empowered governmental body (Bostrom & Sandberg, 2009; Dubljević, 2013a, 2013b; Franke et al., 2015) or a matter for individual clinical judgement (Dubljević, 2013a, 2015; Enck & Ford, 2015). The only exception to this broad grouping is Danaher (2016), who proposes that students could use a form of voluntary 'commitment contracts' where they agree to use enhancements only in certain ways or face punishment (in Danaher's example, focussed on students, this could include docking marks on an assignment). In effect, students become their own gatekeepers by self-limiting their access to enhancements.

The debate around gatekeepers splits down bio-liberal and bio-conservative lines. For example, when considering and rejecting the gatekeeper model Dubljevic (2012b) appeals to citizens' positive right to make decisions about whether to use enhancements or not, and cautions that allowing a clinician to make that decision on behalf of a patient would lack transparency and legitimacy. By contrast, Enck and Ford (2015) – supporters of the gatekeeper model – discuss the role that clinicians could play in guiding patients to make sensible and effective decisions about love and anti-love neuromodulation drugs, arguing that clinicians would have an ethical responsibility to protect patients from seeking a pharmacological modulator to incentivise them to remain in an abusive relationship.

In many ways, however, this analysis does not add a significant amount to existing HTA methodologies where an HTA authority such as NICE or CADTH becomes the 'gatekeeper' for access to medicines. In that respect, the Gatekeeper model can be seen as a particularly well-specified form of the 'no change' position, described next.

3.4.2.5. No change

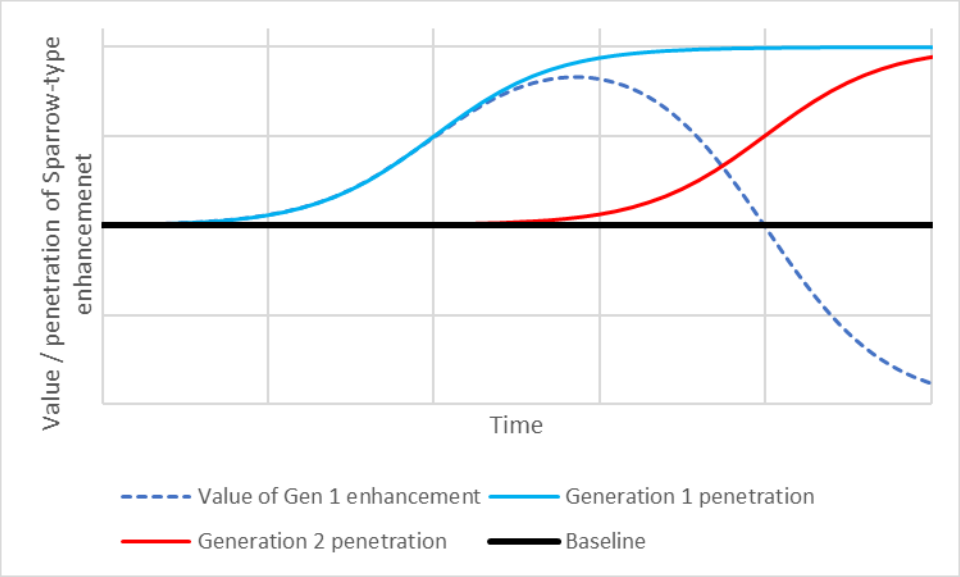
The final category of position where HTA might be possible is where HTA is considered to apply to human enhancement without any required deviation from existing HTA methodology. Chan and Harris (2006), discussing cognitive enhancement, suggest a regulated market where pharmaceutical companies are encouraged to prove the safety and efficacy of their drugs for cognitive enhancement. Maslen et al. (2013) are even more specific that the current HTA model is what they propose, proposing that "medical devices and CEDs [cognitive enhancement drugs] be regulated similarly, in both cases with evaluation of benefits (in terms of increases in wellbeing) and risks". As described in Chapter 2, the concept of NHS Subversion is novel to this thesis and therefore it is unclear if these authors would maintain their position if it meant the end of the NHS as it is conventionally understood.

3.4.3. Conventional HTA not possible

3.4.3.1. Keeler-Cretin paradox

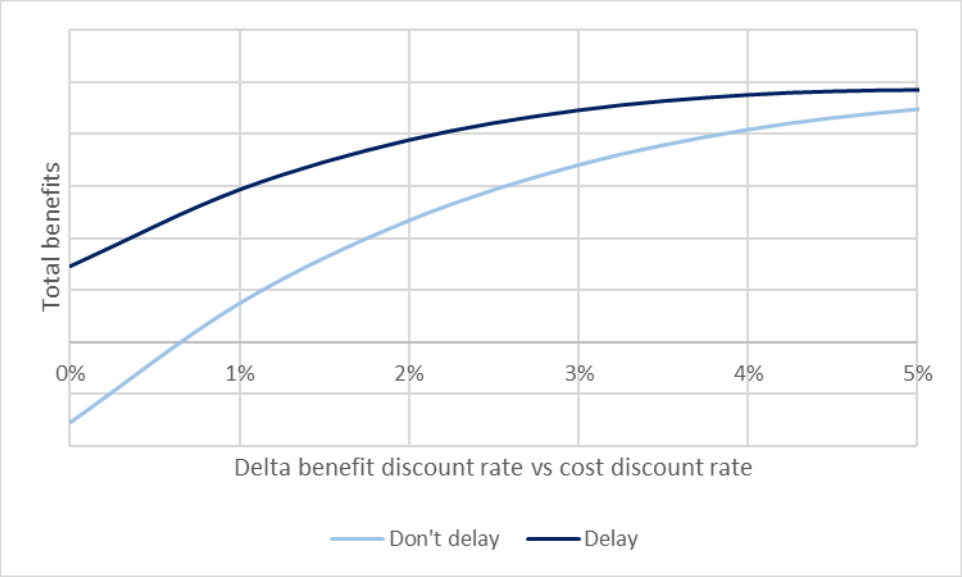
Sparrow (2015) considers what might happen if human enhancement progresses at approximately the same pace as consumer electronics (that is, a significant qualitative improvement every decade or so) and enhancements are largely positional (for example, cosmetic enhancement or cognitive enhancements in some contexts). He observes that this could lead to situations where one's existing enhancements are made obsolete by newer technologies, for example because the new technology is incompatible with the old, because the cost of upgrading is too great to be more than a once-in-a-lifetime event or because conditions that lead to the upgrade being possible no longer obtain (the enhancement may not work on adults with limited neuroplasticity, for example). In these cases, any benefits from enhancement are rapidly offset by time in which a growing proportion of the population is more advanced than you, obviating any advantage once obtained from the enhancement. This notion is demonstrated in Figure 11.

Figure 11 – Value of a Sparrow-type enhancement over time, demonstrating that the initial improvement in performance is rapidly obsoleted



Sparrow's response to this is to recommend the prohibition of these categories of technology altogether, but from a health economic perspective we should consider that responses to the Keeler-Cretin paradox may also be responses to Sparrow's objection (Keeler & Cretin, 1983). Briefly, the paradox states that in situations where the monetary value of health effects is stable over time but the discount rate for health is lower than for costs, cost-effectiveness of an intervention will improve each year the intervention is delayed. In this particular case the discount rate for health is not stable, but it is diminishing after an initial period so after this initial period the paradox will hold. This would imply HTA is impossible, as any intervention with the properties described in Sparrow (2015) must be less cost-effective than the same intervention given a year late (Figure 12), which leads to an infinite chain of delayed decisions.

Figure 12 – Keeler-Cretin paradox applied to example values from Figure 11, demonstrating delaying one step always leads to higher expected benefits (except in cases of extreme discounting, where the initial period dominates)



3.4.3.2. Valuation issues

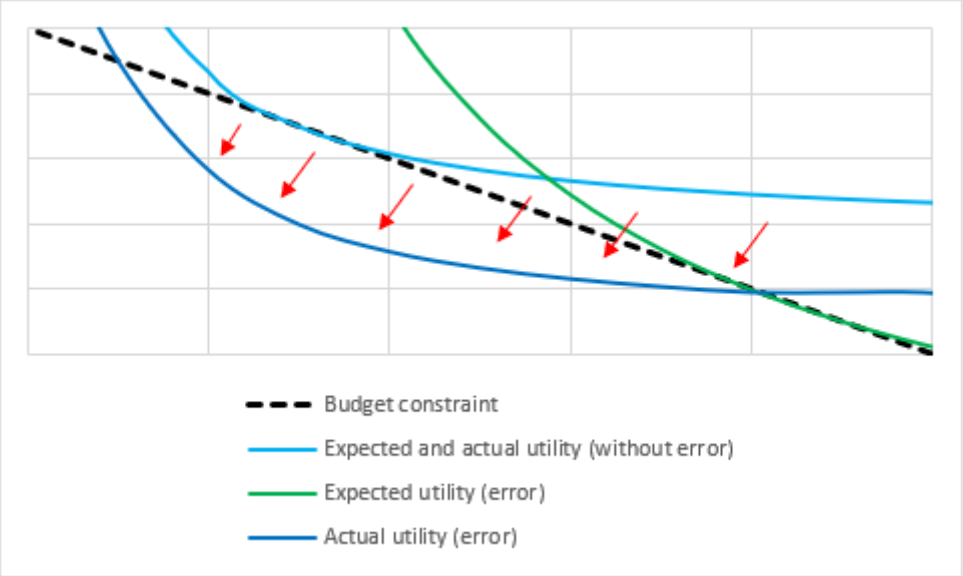
Rajczi (2008) argues that appraisal of enhancement technologies is extremely difficult as a number of cultural and economic forces conspire to lead us to over-value their effectiveness. In particular, Rajczi gives three such forces:

1. Enhancements might be of limited or no value to some but treated as though they have value to all. Rajczi gives the example of a 'mathematics enhancer' given to a warehouse manager who has no interest in recreational maths. Although a 'mathematics enhancer' sounds like the sort of thing with great value, to the warehouse manager it has no intrinsic value as they do not enjoy maths for its own sake, and the enhancement has very limited instrumental value as warehouse managers typically do not become more productive as a result of mathematical training (presumably Rajczi means to say, "After a certain point").
2. Enhancements can be sold to a large population, and so the pharmaceutical industry is sure to launch a persuasive advertising campaign to try and convince people that they need to take enhancements.
3. Enhancements might be come to be seen as an end in themselves, perhaps because of a "quest for meaning" – as reaching the peak of enhanced human 'perfection' replaces other avenues of 'perfecting' the human experience (for example living a perfectly religious or moral life). In health economics terms, a technology might be granted a higher threshold in cost-

effectiveness analysis simply *because* it is an enhancement technology (in a similar way to how innovative technologies are treated as intrinsically valuable in current health technology assessments (Kennedy, 2009))

While points 1 and 2 are issues which are relatively simple to respond to with existing technology appraisal methodologies, point 3 is potentially significant. It is highly interesting that Rajczi (2008) regards the problem in specifically economic terms, unique amongst the publications reviewed here. For example, he points out that "$8000 misspent on enhancements could be used for moral ends… by many calculations it can be used to save 40 or more human lives". The economic logic of Rajczi's position is exactly that; that an overvaluation of some technology leads to inefficient allocation of resources and therefore waste – demonstrated in Figure 13.

Figure 13 – Demonstration of how an incorrect valuation of good Y leads to lower overall utility using Cobb-Douglas function. Red arrows represent utility loss from moving to lower indifference curve



3.4.3.3. Should not be funded by healthcare bodies

A final argument made by Shaw (2014) and Dubljevic (2012a) is that HTA is not possible in the case of human enhancement because it should not be funded by the healthcare system (and thus HTA bodies will have no authority over the decisions which are made). Note that this is not an argument that enhancement should be prohibited; in both models above enhancement is very much allowed, but it is treated as being principally a non-health issue.

In Shaw (2014), the author argues that if it is acceptable to use enhancement technology to redress health inequalities (for example, memory enhancement for people with Alzheimer's Disorder), then it should also be acceptable to use enhancement technology to redress economic inequalities. This could take the form of enhancing the mental and physical characteristics of the socioeconomically disadvantaged, which could then be used directly to compete for better jobs (that is, as a positional good) or could simply be enjoyed for its own sake as compensation for the relatively poorer economic outlook for the enhanced individual (that is, as an intrinsic good). Unlike Ray (2016) in Section 3.4.2.2, Shaw (2014) goes on to consider that the most appropriate budget-holder for this kind of enhancement might be local government, which already has a mandate to reduce inequity *qua* inequity through educational, housing and other programs (note that most healthcare systems are only empowered to reduce *health* inequalities).

Dubljevic (2012a) takes a much stronger position, that justice requires that *no* public funds be allocated to enhancement technologies. This judgement is made on the basis that enhancement would only be undertaken for beneficent reasons, but could lead to unjust outcomes for society (see for example Section 3.4.2.2). Since "justice trumps beneficence", governments must act in a way that avoids injustice if justice and beneficence are in conflict and therefore not allocate funds to enhancement. Dubljevic goes on to discuss the outlines of a system where enhancement might be made available to all without the need for government funds, which has striking similarities to the Economic Disincentives Model he proposes later that year (Dubljevic, 2012b). Dubljevic's position appears to be based on arguments in the disabilities movement (Buchanan, 1996) that are not typically accepted by national HTA agencies and probably require major changes to resource allocation decisions already made, but that if correct would represent a strong reason that conventional HTA would not be possible.

3.5. Discussion

3.5.1. Economic insights from review

Current thinking around enhancements is dominated by bioethicists, who naturally work from a philosophical / ethical paradigm. However, in order to be of value to HTA agencies, these insights must be 'translated' from the language of bioethicists into the language of health economists

(meaning, in this case, mathematical models). While the majority of this 'translation' is motivated and justified in Chapter 4, there are a few subtle points for which the 'translation' needs a little more nuance. These are described below.

3.5.1.1. Externalities are a key economic insight of the review

Externalities are consequences of an economic activity which affect someone other than the agents undertaking that activity, usually in the sense of being harmed. For example landowners are inconvenienced when sparks from a passing railway engine set fire to crops on their land, but are not compensated for this by passengers on the train (Pigou, 2013). Externalities can be positive (as in the case of Outram and Racine (2011a); Savulescu et al. (2011) and Buchanan (2008)) or negative (as in the case of Lamkin (2011) and Goodman (2010)). The range of economic responses to externalities is well studied (Arrow, 1969), and in general HTA bodies have clear guidance on which externalities to consider when undertaking technology appraisal (usually referred to as a 'societal perspective', which is to say considering all possible costs and benefits across society rather than the narrower 'health system perspective').

Externalities feature heavily in the analysis offered by many of the authors in the review. The link is most obvious when considering the 'benefit society' position. Figure 14 demonstrates the economic logic of the 'benefit society' cluster of positions understood as a position on externalities, by illustrating the argument in Buchanan (2008). Under a free market, the quantity of enhancement consumed is too low to be socially optimal. The government can lower the effective 'price' of enhancement by subsiding it, meaning that the quantity demanded is higher and the socially efficient level of enhancement can be reached. If arguments by Lamkin (2011) and Goodman (2010) are preferred, a tax can instead be levelled on the enhancements to reduce the quantity demanded. For arguments such as the public health approach outlined in Outram and Racine (2011a), the same economic concepts are being employed although the level and nature of the tax / subsidy is likely to be more complicated if it is being delivered through a government program rather than through a market mechanism.

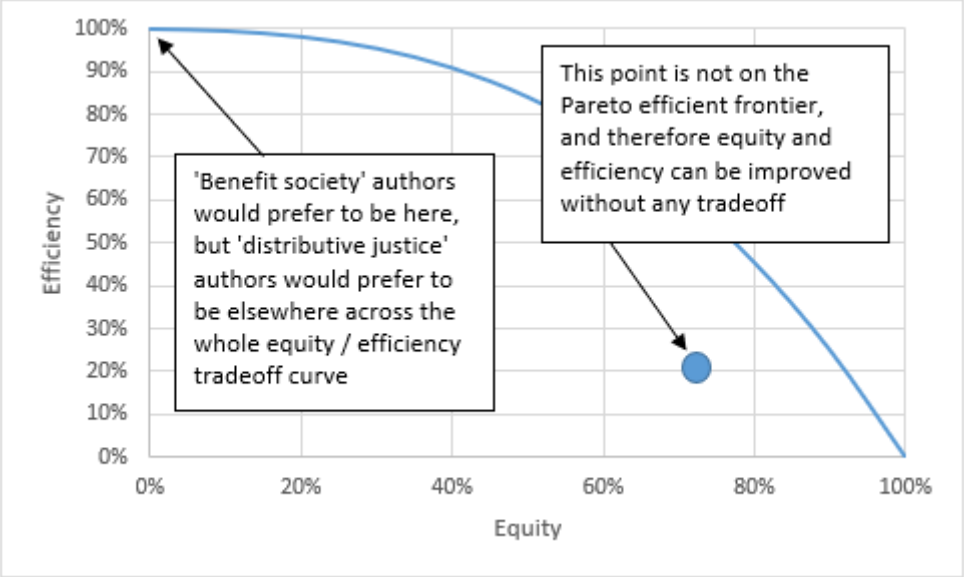
Figure 14 – A simple conceptual model of the argument in Buchanan (2008), taken as representative of the 'benefit society' cluster of arguments. Red arrows represent the direction and magnitude of the subsidy.

3.5.1.2. The equity implications of enhancements go far beyond anything any HTA agency has considered up to this point

Although it is probably fair to say that the mathematical apparatus of QALYs and ICERs described by McCabe et al. (2008) (and in Section 2.2.2) is what most HTA agencies spend most of their time thinking about, in fact it should be reemphasised that most HTA agencies do not act to simply maximise health system efficiency – instead they act to maximise some social value judgement function which includes value for money amongst other more-or-less important parameters (Wagstaff, 1991). A key parameter of this sort is equity, which is defined as "the absence of systematic disparities in health … between groups with different levels of underlying social advantage/disadvantage" (Braveman & Gruskin, 2003), and is so important to the HTA social value function that it is often encountered in a health economics context in the form of the 'equity / efficiency tradeoff' (Wagstaff, 1991). This highlights that after a certain point the only way to make society more equal by some measure is to take the 'winners' and force them to compensate the 'losers'. Figure 15 is a simple diagrammatic representation of the equity / efficiency tradeoff in healthcare, which shows that the 'benefit society' positions of Section 3.4.2.1 are actually just a special case of the more general equity / efficiency tradeoff schema, rather than a conceptually distinct position as it is presented in Section 3.4. In the specific case of this thesis, we are particularly interested in the equity of health outcomes (that is, the distribution of 'health' as an abstract resource

rather than any input that might proxy for health in the real world like number of doctors per capita) and the efficiency of the production of health.

Figure 15 – Simple diagram representing the equity / efficiency tradeoff in healthcare conceptually



There is a caveat to this which is highly relevant to enhancement; the equity / efficiency tradeoff only holds if society is at a productivity frontier. If society is not currently producing health on a Pareto efficient schedule (or if enhancements radically alter the productivity of society) then conceivably it is possible to simultaneously improve efficiency and equity in the distribution of health in society. It is not, however, necessarily possible for health gains to be maximised whilst, for example, ensuring the gap between rich and poor is kept within some acceptable boundary (Lin & Allhoff, 2008). This means that for example the very reasonable claim that more enhancement will lead to inequity which lowers overall utility (arguably, Goodman (2010)) is not actually a meaningful problem for economists since Goodman's argument assumes we are not on a productivity frontier when we enhance. The equity / efficiency tradeoff only occurs when inequity is treated as being bad for intrinsic rather than instrumental reasons.

Since enhancements can potentially radically alter the productivity frontier of the healthcare system, they could in turn radically destabilise the equity / efficiency tradeoff which society has accepted via its social value judgement function. For example, the argument of Ray (2016) would be completely

unthinkable in a pre-enhancement world, since the only way to treat socioeconomic status as a domain of health inequity and then increase equity across the health domain would be to deliberately infect babies of richer parents with some sort of painful disease. However, in a post-enhancement world, the possibility of correcting the unchosen disadvantage of socioeconomic status at birth appears at least superficially more acceptable, meaning that HTA agencies will have to make harder and more consequential equity / efficiency tradeoffs in a post-enhancement world.

3.5.2. Strengths and weaknesses of review

This is the first systematic review of normative literature conducted for use in a health technology appraisal context. Consequently, there are few standards against which to judge the success or failure of the review. As discussed in Section 3.2.1, there has only been one prior review into human enhancement in the HTA context (Wolbring et al., 2013), and this review was conceived and executed in a very different way to the review reported above. Section 3.2.3 highlights that systematic reviews of normative literature are still in their infancy, and therefore comparable reviews in different topic areas are also relatively sparse. With this in mind, the strengths and limitations of the review can be most usefully described by considering how well the review met the objectives identified in Section 3.2.1 and Appendix B.1.1, which is to say how well the review contributed to generation of a health economic theory of emerging human enhancement technologies.

3.5.2.1. Review methodology

The choice of systematic review methodology is a strength of this work. It is clear from the prior experience of Wolbring et al. (2013), the scoping searches conducted for this review in Section B.1.3 and the focus of the literature uncovered in the search that a traditional health economic literature review would have missed several key papers that will go on to form part of a health economic theory of enhancement. It is likely that only Rajczi (2008) and Dubljević (2013a) would have been identified in a conventional literature review, and equally likely that both would have been excluded as their economic insights are not described in a way that is easily translatable to HTA concepts. The ability to articulate theory described in prior literature was greatly strengthened by the ability to cast a wider net to locate that literature, and consider sources not typically included in a health economics systematic review.

It is retrospectively possible to argue that the choice of review method was the correct one. The Review of Reason approach (Strech & Sofaer, 2012) would not have worked well with the type of evidence uncovered in the review. Specifically, almost all included authors made a point about resource allocation in the context of or as part of the conclusion to a wider discussion about another enhancement issue of importance to them. For example, Chan and Harris (2006) discuss five points in their paper, only one of which is related to resource allocation. Indeed, Lamkin (2011) arguably *does not* discuss resource allocation issues, and it is only with the application of an external economic perspective that it is possible to see that the arguments in the publication can be cashed out in terms of externalities. The Review of Reason would – without modification – have fixated on irrelevant reasons in Chan and Harris (2006) (irrelevant in the context of resource allocation) and failed to identify the economic relevance of Lamkin (2011). However, this conclusion is highly specific to the enhancement topic area – more work is needed to identify if one methodology is systematically superior to the other.

3.5.2.2. Comprehensiveness of review

A weakness of this review is that in both practical and conceptual terms it will not have identified every possible position relevant for subsequent analysis.

In practical terms, grey literature was reviewed using 'citation chaining' rather than systematic technique (Sayers, 2008; Talja, Vakkari, Fry, & Wouters, 2007) and therefore this element of the review is non-systematic and difficult to replicate. No relevant papers were included through the citation chaining method, and therefore this weakness is not thought to be profound.

In conceptual terms, evidence in normative literature is different from evidence in empirical literature. Empirical studies are carefully designed to avoid bias and confounding, with different designs known to possess similar characteristic weaknesses, enough to group empirical trial design into a 'pyramid' of evidence (Greenhalgh, 1997). This is not to say that a 'weaker' observational trial design cannot ever be more informative than a 'stronger' RCT (Deaton & Cartwright, 2018), but in general the quality of the trial is equivalent to the quality of evidence – the fewer confounding factors remaining in a trial the closer to the truth the trial is likely to be.

This is not the case in normative literature where arguments may be hypothetical, or counterfactual, or rest on the truth of premises which cannot be proved (Sofaer & Strech, 2012). Weakly supported arguments may be as relevant as strongly supported arguments, and consequently quality assessment performs a different role in normative compared to empirical literature reviews. It is therefore a concern that no reliable method exists to inform readers of the quality of argumentation in a normative paper (it is not even clear that it is possible in principle to sum up the 'quality' of an argument in a single number). This weakness is noted in other examples of the McCullough method (McCullough et al., 2007), and to a certain extent is offset by publication of the full extraction grid in Appendix B.4, but nevertheless represents an area in which future work could improve upon this review.

3.5.2.3. Inclusion and exclusion criteria

The review was made considerably more complex than previous systematic reviews of normative literature by the need to interpret philosophical works through a health economic lens in order for the publications to be of value to decision makers. McCullough et al. (2007) note this problem, identifying that there is no consistent standard for referring to the concept of 'concealed medicine', an issue that was similarly observed with the concept of 'resource allocation'. However, while McCullough et al needed only to find the synonym for 'concealed medicine' that was used, this review required interpretation of the content of a publication to understand if a claim about resource allocation was actually being made. Because of this, best practice in systematic reviews of having a second reviewer validate the decisions of the first on a subset of papers (Petticrew & Roberts, 2006) was not followed – the domain knowledge needed to effectively review papers was too specialised.

This domain-specific knowledge requirement should lead us to question whether the inclusion / exclusion criteria were a weakness of the review. Certainly, there were a number of publications excluded and included at the margin where a case could have been made for the other decision. For example, two papers were included on the basis that they advocated for no change to existing HTA systems (Dubljevic, 2012a; Shaw, 2014). However, many more publications argued for 'regulation' of enhancement in a general sense (Berg, Mehlman, Rubin, & Kodish, 2009; Outram & Racine, 2011b;

Savulich et al., 2017), which is at least *consistent* with a policy of no change if not an explicit acknowledgement of such. More provocatively, perhaps any paper which is on the topic of enhancement but which does not call for a change to the process of resource allocation could be thought of as endorsing the current system of resource allocation. On the other side of this margin, papers such as Lamkin (2011) and Sparrow (2015) were included despite not featuring any obvious resource allocation content on the principle that they clearly described important health economic principles in different conceptual language. However, this raises the possibility that other exclusions were unreasonable, since in some sense they could possibly be linked to an economic principle. For example, Thau (2020) describes how cryonics may lead to negative outcomes if future civilisations chose to torture the recently unfrozen. This could perhaps be modelled as a strongly nonlinear (or perhaps discontinuous) change to the discount rate, but there is really nothing in the publication that supports the idea that the concept is being presented in terms of resource allocation. The paper was therefore excluded on the grounds that the review was intended to identify literature with a resource allocation component, rather than extend the work of other authors until a resource allocation argument could be made – but as there is no definite cut-off for the difference between reporting a concealed resource allocation point and extending a paper to cover a point that was not there to begin with, the decision was debatable.

Overall, concerns about the inclusion and exclusion criteria represent the greatest threat to the reproducibility of the review. However, they do not represent a significant concern for the purpose of the review, which is to identify and taxonomize positions that could be relevant to developing a health economic theory of human enhancement in a health technology context; it is highly likely that the extensive inclusion criteria and systematic approach to review have identified all major positions in the literature of relevance to the review. Compared to the McCullough method example paper (McCullough et al., 2007) quality of included papers was similar (an average of 2.8 in McCullough et al. (2007) vs 3.1 in this review), and the discrepancy is reasonably straightforward to explain in that the scoring criteria for this review set out in Figure 44 in Appendix B.4 allowed certain papers to score partial points they could not have picked up in McCullough et al. (2007).

3.6. Conclusions

In recent years, there has been interest in developing and extending the principles of systematic review to cover argument-based or normative ethical questions (McCullough et al., 2007). Methodologies are still being developed for this expanding field of study (McCullough et al., 2004; Strech & Sofaer, 2012), but the case for using a systematic review to inform health economic work in human enhancement was sufficiently strong that use of an atypical technique was justified. The 'McCullough Method' (McCullough et al., 2004) was applied to a broad systematic search of eight databases, supplemented with hand-searching the grey literature via the 'citation chaining' approach (Sayers, 2008; Talja et al., 2007).

The review has helped crystallise current thinking on human enhancement and resource allocation, and will be invaluable in taking the next step of formally specifying a coherent health economic theory of the technology appraisal of enhancement technologies. The choice of adopting systematic review methodologies in a field traditionally dominated by narrative reviews was of great value, since it has helped organise a very large and disparate literature base into a sensible framework, and then put that literature base to work in an economic context. Six conceptually distinct groups could be identified and (see Table 4), and these six positions form the basis of the remainder of this thesis.

Positions in the review vary, but the weight of publications propose that human enhancement does present specific and important resource allocation issues. These range from unique externalities and unique equity issues to specific models of resource allocation such as the Economic Disincentives Model. The preponderance of studies raise issues that can be regarded as minor modifications of HTA methods (or, in the case of Savulescu et al. (2011), issues of parameterisation rather than conceptualisation). However, the publications which do raise objections to HTA (Dubljevic (2012a); Rajczi (2008); Shaw (2014); Sparrow (2015)) should be taken extremely seriously since, unlike conventional clinical evidence, a single strong counterexample can bring down centuries of accumulated philosophical thought overnight. For example, the definition of knowledge as 'justified, true belief' was thought to be a 'solved' problem in epistemology until the publication of Gettier's famous 1963 paper (Gettier, 1963; Hetherington, 2011). A review undertaken in 1962 would reach a

radically different conclusion to a review undertaken in 1964. Similarly, if – for example - Sparrow (2015) had been excluded from this review, it would have reached radically different conclusions by missing the link between obsolescence and the Keeler-Cretin paradox.

Note that two obvious positions not discussed until now are that human enhancement should be made available to all over the counter (referred to as 'laissez-faire' by a number of authors such as Bostrom and Sandberg (2009) and Outram and Racine (2011a)) and that human enhancement should not be allowed under any circumstances (referred to as 'prohibition' in general – see for example Dubljević (2013a)). These positions are clearly relevant in the broader human enhancement debate, but from a health economics perspective if there is no moral basis on which a government could respectively prohibit or allow enhancement technologies to be given to the population then there is no purpose to health economic analysis because there is no tradeoff between competing uses of resources. These 'degenerate' positions (meaning that one value in the complex web of trade-offs representing economic analysis of a healthcare technology is made to take a zero value) were explicitly excluded by the review criteria, since they do not represent a serious attempt to allocate resources in conditions of resource scarcity, but should – of course – not be overlooked in the actual public policy debate around enhancement technologies or in analysis of possible NHS responses in Chapters 4 and 5.

Although the most notable absence from the results is excluded by design, there were a number of unexpected omissions from the literature review. For example, the concept of enhancing the intellect of professional academics was only touched on by one anonymous submission to the editor of *Bioethics* (Anonymous (2009) - excluded for not describing a resource allocation issue), which seems a surprisingly outward-looking omission given that the included publications are written mostly by academics. Similarly, the effect of enhancement on areas of very major concern to economists such as international trade, interest rates, productivity and so on are not included in the review, or really substantially in any excluded study. One significant omission which leads to a highly novel finding in Chapter 5 is that all authors appear to imply that enhancements will all be of a similar type – which is to say they will all enhance along some specific axis which represents the 'enhancement' of a person.

In fact, modern medicine is not like that – there are many varieties and types of medicines that act and interact in different ways – and so this seems like an important omission from the general literature.

Overall, the major finding of the review is that there are only two potentially insurmountable challenges to developing a health economic theory of human enhancement – that discount rates might be too unstable for any meaningful economic evaluation to be conducted (Sparrow, 2015) and that valuation of enhanced health states might be impossible (Rajczi, 2008). Arguments that the public health system should not pay for enhancements would also be insurmountable from the perspective of actually implementing a health economic theory of enhancement, but not from the point of view of developing the theory, so the objections of Shaw (2014) and Dubljevic (2012a) are seen as less fundamental. It is highly likely that any theory which is developed will have to content with unique externalities - both in terms of scope (Savulescu et al., 2011) and scale (Lamkin, 2011). Further, issues of economic equity are likely to be exacerbated by the fact that enhancement is both an intrinsic and instrumental good (Ray (2016) and Lavazza (2019)).

Chapter 4. Health economic modelling of human enhancement

4.1. Chapter Summary

As with Chapter 2, this Chapter is somewhat long and conceptually complex. While broadly describing the theory and parameterisation of an economic model, it may be easier to describe as being split into two semi-distinct parts:

1. The first part, consisting of Sections 4.2 to 4.4, describes how the economic model is to be created. The use of economic models to 'build theory' (Dekkers, Barlow, Chaudhuri, & Saranga, 2020) through the use of counterfactual economic modelling is potentially a controversial approach within the discipline of health economics, and so the ontology and epistemology of the model is explicitly spelled out in some detail.
2. The second part, consisting of Sections 4.5 to 4.7 is the actual project of 'translating' the bioethical arguments from Chapter 3 into formal mathematical descriptions of a health economic system, and hence effectively represent the first-order results of the modelling.

This Chapter should be seen as a companion piece to the economic model provided as Supplementary Material.

4.2. Ontology and epistemology

4.2.1. Simulation vs analytical modelling

The purpose of this Chapter is to develop a rigourous theory of the benefits and drawbacks of funding particular enhancements, across a range of enhancement scenarios identified in Chapter 3 . Experimental or observational approaches are therefore ruled out, since human enhancement techniques do not yet exist to a significant enough degree that their impact on HTA can be measured. Therefore, it is necessary to 'build theory' using an economic modelling approach (Dekkers et al., 2020). In economics (and by extension, health economics) there is an extremely well defined method of theory development and articulation through modelling that would probably be considered 'standard' in the field, which is to say mathematically proving that certain results follow from certain key economic assumptions which are considered to be uncontroversial (Varian, 1992). For example,

one could reasonably argue that the field of health economics was developed by applying standard economic assumptions to an unusual good – health – and formally modelling the results (Arrow, 1963). Attempts to deviate from this ontology are regarded as heterodox at best and are more usually regarded critically (Lehtinen & Kuorikoski, 2007). Nevertheless, I argue in this Section that developing a health economic theory of a good which does not yet exist – enhancement, in this case – *requires* an alternative theoretical approach, and therefore spend some time outlining the ontological and epistemological pre-commitments of this Chapter below.

The approach which will be adopted in this research is a simulation approach. A simulation approach is the process of "imitating an economically relevant real or possible system by creating societies of artificial agents and an institutional structure in such a way that the epistemically important properties of the computer model depend on this imitation relation" (Lehtinen & Kuorikoski, 2007). The authors note that this is a definition which applies to simulations in economics (a discipline characterised by the interaction between agents and structures) but not necessarily 'simulations' in general. A more general definition is given in Hartmann (1996), who argues that a simulation is an imitation of a process within another process. An intuitive way of thinking about simulation in economics is to consider it the creation of 'artificial societies' of simulated individuals interacting with each other (Gilbert & Conte, 1995).

The main alternative to simulation which allows for the assessment of counterfactual scenarios is computation. Computation is otherwise known as algebra / formalism and attempts to rigorously prove a relationship between two or more variables. The distinction between 'simulation' and 'computation' is clearly drawn in the literature (Winsberg, 2003); a 'computation' is an analytical process which just so happens to use a computer to automate otherwise tedious problem solving, whereas a 'simulation' is a quasi-experimental (Winsberg, 2003) or even genuinely experimental (Gilbert & Troitzsch, 2005) process which aims to mimic some feature of the real world using a computer as a substrate. In practical terms, computation is described as being aimed at theory articulation (proving some relationship between pre-existing elements of a theory) whereas simulation is described as being aimed at theory generation (developing a theory about the imitated agents and

system by varying their characteristics and observing the results) (Lehtinen & Kuorikoski, 2007) – although it is not clear this distinction really stands up to rigorous scrutiny, as there are famous examples of simulations which can be conducted by hand such as the Schelling Tipping Model (Schelling, 1978) and equally famous examples of agent-based models which can be solved analytically such as the 'Market for Lemons' (Akerlof, 1978), but as a guide to discussing the issue over the next few paragraphs the distinction seems reasonable.

An important distinction between computation and simulation models is that simulation models allow for (but do not automatically lead to) the phenomenon of 'emergence' (Gilbert & Troitzsch, 2005). Emergence is when a system has properties which are not found in any of its constituent parts (Hodgson, 2000), which is often summarised as higher-order phenomenon emerging from lower-order phenomenon. For example, in Schelling's Tipping Model a mix of black and white agents follow simple and non-racist rules such as, "Move house if you are a minority in your neighbourhood" but the end result is extreme racial segregation – within a few generations almost no agent lives in a racially mixed neighbourhood (Schelling, 1978). This is an absolutely critical property of any investigation into human enhancement; a recurring theme in the literature is that enhancements may offer tempting benefits for humanity but the second-order effects are likely to be unacceptable. For example, Lamkin (2011) proposes an emergent function of enhancements which echoes Schelling's original work – if being a minority leads to hardship in proportion to the size of the majority and enhancement offers a way to become indistinguishable from the majority group, then some minority agents may choose to use this enhancement to become members of the majority, which further increases the pressure on remaining minority agents to change and so on in a vicious circle which ends with the loss of entire minority groups. In economics there is some debate about whether emergence truly exists since the low-level phenomenon are humans and humans are typically viewed as entirely sovereign over their choices (Douglas & Kontopoulos, 2012). However, this is an extremely complex debate which does not advance our understanding of human enhancement – since we can learn novel things about agents and systems by simulating them in contrast to merely

analysing them there is clearly value in this approach whether we call this new information 'emergent' or not.

4.2.2. Challenges to simulation modelling

On balance, the economics literature is quite unforgiving towards simulation modelling compared to computation (Lehtinen & Kuorikoski, 2007). In the sense that simulation modelling is in contrast to computational analysis, simulation modelling entirely sidesteps two fundamental tools in an economists' arsenal – rational actor theory and the principle of solving for equilibrium (Lehtinen & Kuorikoski, 2007). Lehtinen and Kuorikoski (2007) go on to claim that simulation modelling is only fully accepted when one or both of these principles is known not to hold, for example in finance where certain empirical puzzles cannot be solved with reference to these approaches (LeBaron, Arthur, & Palmer, 1999). There are ontological and epistemological reasons that explain why economists are wary of simulation approaches:

4.2.2.1. Ontological challenges

Ontologically, simulation models abstract away much of what makes human interaction complex. Gilbert and Troitzsch (2005) point out that a modelling technique which can be applied interchangeably to humans or ants probably fails as a description of humans rather than speaking to the intelligence of ants. A demonstration of this problem occurs when simulation models are extended into areas where empirical evidence is inadequate such as when making predictions about the future; whereas one of the great strengths of equilibrium theory is that it is presumed to hold in all possible situations, simulation modellers must encode radical assumptions about the kinds of behaviour which will be exhibited in these societies in the absence of evidence that entities in that society will actually behave in that way (Lehtinen & Kuorikoski, 2007).

To identify why this might be a problem to economists, consider the distinction between 'normal science' and 'paradigm shifts' identified by (Kuhn, 1973); one of the major problems with science is that scientists need to hypothesise the existence of certain entities to do any useful work, and if these ontological pre-commitments prove to be empirically inadequate it leads to a scientific revolution. Economists do not need to hypothesise the existence of any entities to solve algebraic equations using

data collected empirically unless they are simulation modellers, and therefore can do 'normal science' without fear that their work will be overturned, whereas simulation modellers are at very great risk of a paradigm shift overturning their work.

This objection is extremely relevant to this research as enhancements do not yet exist in a significant fashion and therefore research into their properties is extremely likely to be based on flawed assumptions about what they will be like.

4.2.2.2. Epistemological challenges

Epistemologically, the simulation plays the same role as algebra would in a more conventional analytical proof (Judd, 2001). Yet the simulation is orders of magnitude more difficult to check for consistency and accuracy than algebra – each line of code must be carefully scrutinised as assumptions may be smuggled into the most innocuous elements.

Even if the code is error-free, statements about the results of the model can only be understood in the context of the computer substrate the model has been run on – the problem of scientific underdetermination which would not otherwise trouble economists (Duhem, 1991). Lehtinen and Kuorikoski (2007) point out that there are mathematical proofs which have only been proven with the aid of a computer simulation (Tymoczko, 1979, quoted in Lehtinen & Kuorikoski, 2007), but it is not clear this is an adequate response - Tymoczko (1979) makes it clear acceptance of this proof is a major point of contention in the mathematical community and appears to reinforce that in 'harder' sciences such as mathematics, simulation approaches are only acceptable when no other option can derive the necessary output.

Finally, the results of simulation are 'clunky' in the sense that they can only be used as a parameter input in a future simulation (Backhouse, 1998); an algebraic proof can be neatly slotted into future proofs as and when necessary. For example, Central Limit Theorem is one of the most important results in econometrics (and statistics more generally), and a number of neat algebraic proofs exist for it (Kwak & Kim, 2017). Papers which invoke Central Limit Theorem do not have to re-derive it each time it is needed because it is understood that a single algebraic proof means that the theorem remains proven in all situations. A simulation model which discovered the Central Limit Theorem as an

emergent consequence of adding independent random variables would be useless for this purpose, and therefore the use of simulation greatly circumscribes the purposes to which a result can be applied.

4.2.3. The appropriateness of simulation modelling to enhancement research

Overall, despite the spirited defence of simulation modelling offered by Lehtinen and Kuorikoski (2007), these objections are extremely troubling. Although there are clearly cases where simulation modelling is superior to computational proof such as the ability to simulate certain highly reflexive or otherwise complex human processes like 'rationality' (Elster, 1986), or the learning exhibited by a back propagation neural network (Hecht-Nielsen, 1992), these cases are presented as exceptions in the literature, supporting the idea that simulation is what is done when better methods are not available. In fairness to simulation modellers, they have robust responses to these criticisms; for example, a discovery which holds across all possible societies is effectively a law of human behaviour and therefore no conceivable empirical evidence could affect it, making it equivalent to an algebraic proof. One could also take the view that rational actor theory and general equilibrium are strong assumptions which should not be automatically assumed true for the sake of the convenient results they generate. For example, rational actor theory has come under sustained empirical criticism (Kahneman & Tversky, 2013). Therefore – potentially – simulation modelling is no worse than any other economic tool in terms of the assumptions it embeds in its models. Some authors go further and argue that the actual truth or falsity of assumptions in economic models are subordinate to their ability to highlight deep underlying relationships which would otherwise have gone unnoticed (Friedman, 1953), which would be a strong theoretical reason to prefer simulation to computation (although most economists do believe that true assumptions are at least somewhat important, at least for critical parameters (Hindriks, 2005)).

For this research, however, simulation modelling appears to be an appropriate investigative tool. First and foremost, an analytical approach would be extremely challenging; there are substantial limits on what can be accomplished with an equilibrium approach in the absence of any data to populate algebraic equations since the research describes a hypothetical future technology about which almost no information is known. Since all authors agree simulation is a reasonable approach when no other

approach is possible, the decision to simulate is consistent with the literature on this point (Kwakkel & Pruyt, 2013). Secondly, the value of the research is unlikely to be in deriving general rules about the assessment of human enhancement technologies, but rather to identify characteristic breakdowns of existing HTA assumptions when applied to certain kinds of technology. Therefore, criticisms over the lack of 'portability' of simulation models are not relevant in this context; the standard of proof required for this research to be useful is really only that it is empirically adequate rather than meeting the standards of a conventional theorem proof. Finally, the objection that simulation creates entities which ideally shouldn't exist in economic theory is not relevant in this case; the research focusses on the features of hypothetical entities (hypothetical healthcare technologies) and therefore any reasonable analysis of the work will necessarily consider the sorts of (conjectural) entities that result in certain outcomes.

Therefore, the key reasons why a simulation approach is appropriate for this investigation are:

- The consensus in the literature is that simulation can provide adequate justification for theory generation, which fits with the overall objective of this research as being 'theory building' (Dekkers et al., 2020) rather than verification of an existing theory.
- There is an existing literature on how to adapt simulation models into societies which do not exist (so-called 'artificial societies' (Gilbert & Conte, 1995)). This includes societies with enhancement-like characteristics (Doran, 1997).
- The dynamics of a simulation will allow for emergent effects to appear as described in the literature on human enhancements (Gilbert & Troitzsch, 2005)
- The very real and significant drawbacks of simulation modelling are limited in this case because of specific features of the research. Specifically: ontological objections about creating entities which wouldn't otherwise exist are limited because we actually want to speculate about those entities in this case, and epistemological objections about the 'clunkiness' of investigations undertaken in a simulation framework are limited because there is no intention to make the research portable – there is a very narrow focus to just an early

investigation into healthcare spending decisions made in a very specific cost-effectiveness framework.

4.3. Methodology

4.3.1. Types of simulation approach

Gilbert and Troitzsch (2005) propose that there are seven kinds of simulation model. Their taxonomy varies depending on the number of levels of agent that can be modelled, whether agents can communicate with each other, how complex the agents are (apparently based on the subjective judgement of the authors) and how many agents can be simulated. Based on Gilbert and Troitzsch (2005)'s taxonomy, we can make certain restrictions to the type of simulation model that could be appropriate for a health economic theory of human enhancement:

- The number of levels must be at least 2 – individual agents must influence the decision which an HTA body takes, and in turn this decision must influence outcomes at the individual level
- For the purpose of this research, communication between agents is irrelevant - it is a reasonable assumption that people's decisions about their healthcare does not depend on decisions others make, although in practice the situation is somewhat more complicated than this (Grinyer, 1994) and it is possible to imagine that some enhancements may become 'fashionable' in a sense that would mean communication between agents is relevant (Rajczi, 2008). Nevertheless, it is not really clear what or how agents would communicate about enhancements without more empirical work understanding people's likely reaction to them, and so this possibility cannot be included in this model. If communication between agents is irrelevant then the principle of making the model as simple as possible suggests non-communication is to be preferred if appropriate (Varian, 2016).
- The complexity of agents must be high to account for flexibility in the theory generation process. One could easily argue that it is only convention which keeps the agents simple in a Queuing model (unlike in a multi-agent model where the agents must be simple by design for computational reasons) and that Queuing models can exhibit very sophisticated agents if the demands of the problem call for it, especially in healthcare (Günal & Pidd, 2010). However,

as Queuing models are unsuitable for other reasons there is no particular value in disagreeing with Gilbert and Troitzsch (2005) on this point.

- The number of agents must be large, since in principle the simulation will be of the entire NHS. In principle there is no reason why a multi-agent model could not be extended to cover the entire NHS, but in practice the computational resources required would be totally infeasible, so a partial success here is insufficient.

Table 5 summarises these approaches, and applies colour coding to indicate whether each parameter would be appropriate for this research against each model type.

Table 5 – Types of simulation model from Gilbert and Troitzsch (2005) and their appropriateness to the research question indicated by colour coding

	Number of levels	Communication between agents	Complexity of agents	Number of agents	Suitable?
System dynamics	1	No	Low	1	No
Microsimulation	2	No	High	Many	Yes
Queuing model	1	No	Low	Many	No
Multilevel simulation	2+	Maybe	Low	Many	No
Cellular automata	2	Yes	Low	Many	No
Multi-agent models	2+	Yes	High	Few	No
Learning models	2+	Maybe	High	Many	Yes

Potentially appropriate | Complex / see discussion | Likely inappropriate

Applying these restrictions indicates that either a microsimulation or a learning model would be an appropriate simulation approach. A learning model is a type of artificial intelligence which modifies its basic parameters in response to being told whether its guesses are correct or incorrect – for example, a backpropagation neural network is a relevant kind of learning model (Hecht-Nielsen, 1992). This could potentially be important if there was an extensive empirical literature on the topic of public acceptance of health-related human enhancements, since the model could be trained to match public sentiment regarding enhancements. There is some literature of this kind (e.g. Fitz, Nadler, Manogaran, Chong, & Reiner, 2014), but data are not available of the kind and quantity needed to populate a learning model and therefore a learning model would not be suitable for reasons of training data availability. This does however suggest a novel method of developing a health economic theory

of human enhancement which is not covered in this research; a learning model could be created based on the input of the UK public and we could use the judgement of this model in place of a conventional decision rule. Although an interesting idea to speculate about, this would so radically redefine the nature of HTA bodies we might consider if this is the only possible solution that in effect there is no solution within the existing HTA framework – therefore this idea is not discussed any further.

If learning models are excluded for reasons of data suitability, microsimulation modelling remains. Microsimulation models are approximately the simulation modelling analogue of a deterministic discrete state-transition model in more traditional computational economics (Krijkamp et al., 2018). It is often referred to by the slightly incorrect name of 'Monte Carlo simulation' (Zagheni, 2015), in an analogous manner to how discrete state-transition models are often referred to as 'Markov Chain simulations' despite not all state-transition models sharing the Markov assumptions (that is, all Monte Carlo simulations are microsimulation, but not all microsimulations use the Monte Carlo method) (Briggs, Sculpher, & Claxton, 2006). One aesthetically pleasing element of selecting microsimulation as the simulation approach is that microsimulation has been used in a number of NICE submissions (e.g. NICE TA599, 2019) and therefore assumptions made in the modelling element of this research can be tested against assumptions made in actual HTA submissions for validation (this observation further highlights the artificiality of the distinction between computational and simulation approaches in the literature – for the purposes of HTA the microsimulation in TA599 is treated as epistemologically equivalent to an equivalent computational model!)

4.3.2. Microsimulation modelling

To briefly explain and motivate the microsimulation approach, consider the modelling problem faced by Si et al. (2019), a paper with an entirely typical microsimulation approach but uncommonly good explanation of why the approach was appropriate. They wanted to perform a health economic evaluation of osteoporosis interventions, and so note that a Markov model would commonly be used to allow patients to enter the 'fracture' disease state chronically over time. This is depicted in Figure 16a, and would be a trivially easy model for any first-year economics student to solve. However, their review of the literature finds that after the first fracture the chance of a subsequent fracture "varied by

sex, fracture site and BMD [bone mineral density] level" (Bliuc, Alarkawi, Nguyen, Eisman, and Center (2015), quoted in Si et al. (2019)). If we wish to model the full complexity of this, we would have to create a model structure like Figure 16b, which is an almost intractable tangle of conditional transitions – an error in any one of which will result in incorrect or even nonsensical results. The solution described by Si et al. (2019) is a microsimulation approach conceptually related to Figure 16c; use algorithms and interpolation to create multiple possible patient pathways, and then take these patient-level results in favour of population-level results. It may not be completely obvious to non-economists that the model structure in Figure 16c is significantly more straightforward than the model structure depicted in Figure 16b, but it should be clear that the difference between the two is that Figure 16b has to be created entirely by hand by a human (which is labour intensive and error-prone) whereas Figure 16c is exactly the same simple approach as Figure 16a, just repeated thousands of times with minor variations – a task a computer can carry out in a few seconds without any risk of error.

Figure 16 – Conceptual diagram motivating the choice of microsimulation model vs complex discrete-state model for modelling osteoporosis

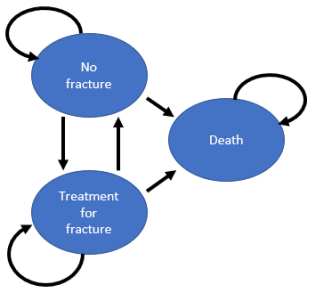


Figure 17a
Ordinary discrete-state transition model. Computationally straightforward, but incorrect in osteoporosis

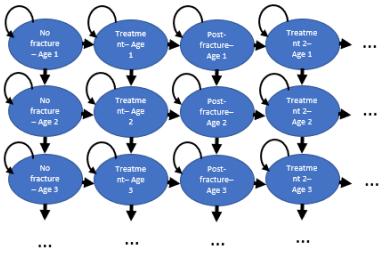


Figure 17b
Attempt to model the entire complexity of the osteoporosis pathway using discrete-state transitions. Shown is an incomplete 2-dimensional matrix with no absorbing states – a genuine attempt at this problem would be orders of magnitude more complex

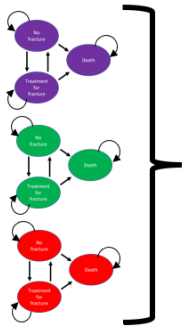


Figure 17c
Microsimulation model, demonstrating how the output of multiple simple discrete-state models can be combined to produce the same result at Figure 17b

The methodological approach to microsimulation modelling is conventional in the health economics literature (Briggs et al., 2006). In broad terms, the process of creating a microsimulation model requires three inputs (Dodds, 2005):

- The ‘demand’, which in healthcare modelling will be represented by the incident patient population
- The ‘process’, which Dodds (2005) defines as being the “pathway or sequence of actions” applied to each unit of demand. In this model the ‘process’ will be represented by the healthcare system’s response to each patient.
- The ‘capacity’, which is the resources required to undertake the process.

The demand and capacity element are straightforward to describe, since the work will follow accepted methods of technology appraisal (McCabe et al., 2008), for example the NICE Methods of Technology Appraisal (NICE, 2013), which describes the process (fully incremental cost-effectiveness analysis) and the capacity (£20,000 - £30,000 per QALY) in sufficient detail for replication. The process element is the element which will be varied in modelling, and is described in more detail in Appendix C.1.

4.3.3. Assessing model outputs

4.3.3.1. Unitary criteria decision making is inappropriate

Implicit in this description of the simulation process is that it is possible to recognise good from bad outcomes when viewing the model outputs. For example, in Dodds (2005) objective outcome measures like resource use and waiting time are used to judge good from bad outcomes. This is consistent with the vast majority of the literature on the topic (Kuljis, Paul, & Chen, 2001; Lehaney, Clarke, & Paul, 1999; Lehaney & Paul, 1996; Page et al., 2000). If it is *not* possible to recognise good from bad outcomes (algorithmically) then it is not possible to use algorithmic methods such as simulation modelling to determine whether a particular approach to enhancement is likely to be superior to some other approach.

A naïve approach to this problem would be to note that in cost-effectiveness analysis there is a single factor which dominates health technology appraisal – cost-effectiveness – and assert that therefore it is possible to treat this as the sole output of the model of relevance to assessing approaches to enhancement. This would not be an appropriate approach for a number of reasons:

- While cost-effectiveness is clearly important, not all NHSes have explicit cost-effectiveness thresholds, and even in systems where the threshold is explicit technologies are sometimes approved above the conventional higher end or rejected below the lower end of this (Devlin & Parkin, 2004)
- HTA methods explicitly allow for factors outside economic efficiency – such as equity, innovation and uncertainty – should factor into the decisions their committees make (NICE, 2013)
- Optimising for cost-effectiveness alone would simply generate a restatement of the problem of NHS Subversion, since this is a known problem with consequentialist approaches. The purpose of this work is to try and develop a theory of enhancement which is not vulnerable to utility monsters, and an approach which does not recognise this must be flawed.

A more sophisticated approach would contextualise HTA decisions in their broader position as a kind of health policy decision. Healthcare policy decision typically do not have clear and obvious *ex post* states which can be objectively compared against each other (Hanberger, 2001), and generally optimising across a single unitary dimension will not capture all elements which are relevant to healthcare policy-makers (Baltussen & Niessen, 2006). The decisions which HTA bodies must usually manage are atypical in this respect; the significant theoretical work performed by the QALY means that decisions facing HTA bodies usually do have clear and obvious *ex post* states which can be compared against each other (Whitehead & Ali, 2010). However, if the boundaries of the decision problem facing the HTA body go outside the assumptions which inform theoretical work around the QALY (in this case, the assumption that quality of life will always be ≤ 1) then the outcomes once again become impossible to straightforwardly compare – although to be clear this criticism is about comparing different 'currencies' against each other (health efficiency vs health equity, for example) rather than the difficulties of measuring hard-to-define outcomes in a health context (what *exactly* is equity, for example). The difficulty of doing the latter is very well noted (Braveman & Gruskin, 2003), but is not directly relevant to this thesis.

A standard method of assessing the quality of healthcare reforms with harder to measure outcomes is a qualitative interview with key contemporaneous stakeholders (Beaussier, Demeritt, Griffiths, & Rothstein, 2016), and this method has been successfully applied to UK NHS reforms that introduced NICE (Timmins, Rawlins, & Appleby, 2017), implying that it would be suitable to assess variations to HTA methods too (given that NICE are usually regarded as front-running other HTA bodies with respect to their methods (NICE, 2002)). While there are some authors who assert that qualitative interviews could be used as an inferior alternative to simulation models (Ramsey, McIntosh, Etzioni, & Urban, 2000), this would not be suitable for a simulation approach of a future technology for a variety of reasons – most obviously that retrospective interviews on an event which will occur in the future is logically a contradiction in terms and logistically it would not be possible to individually evaluate each of the tens of thousands of possible simulations planned in a qualitative fashion.

4.3.3.2. Multiple Criteria Decision Analysis is required

Recognition of this problem – which exists in a number of fields (Dodgson, Spackman, Pearman, & Phillips, 2009) - has led to a serious effort to develop a methodology which can "take explicit account of multiple criteria in helping individuals or groups explore decisions that matter" (Dodgson et al., 2009). Broadly defined, this methodology is known as 'Multiple Criteria Decision Analysis' (MCDA) (although note that this is an umbrella term covering at least three separate methodologies (Thokala et al., 2016) and an almost innumerable number of methods (Zanakis, Solomon, Wishart, & Dublish, 1998)). The approach is most usually associated with operations research, although its use in healthcare is growing (Diaby, Campbell, & Goeree, 2013) – most notably by the ISPOR group already cited (Thokala et al., 2016). Moreover, this approach has been used in a purely hypothetical exploration of healthcare resource allocation, making it a good match for this project (James, Carrin, Savedoff, & Hanvoravongchai, 2005).

The principles of MCDA decision making are to enumerate criteria which are important to the decision, weight those criteria according to their importance and then combine the final scores per criteria via a weighting algorithm to reach a final judgement (Devlin & Sussex, 2011). This decision-making algorithm could be made more complex, for example using an 'outranking' model where

hierarchies of importance are pre-defined, and then iterated elimination of dominated alternatives at each level of hierarchy is employed (Baltussen & Niessen, 2006). However, there seems to be no consensus in the literature as to whether these more complex methods provide superior judgement (Zanakis et al., 1998) and therefore it is appropriate to use the simplest methods which are suitable.

This process itself is challenging, and perhaps the reason formal adoption of MCDA has been slow to date; there is no existing literature attempting to quantify the weights society attaches to various criteria that might inform an HTA decision (all existing literature is ordinal at best – see NICE (2004)). Even if such weightings did exist, one reason for using the MCDA family of methodologies is that it explicitly takes into account elements of value judgement such as societal preferences or political considerations (Goddard, Hauck, Preker, and Smith (2006); Wiseman, Mooney, Berry, and Tang (2003) respectively, both quoted in Baltussen and Niessen (2006)) As both societal preferences and political considerations may change radically following the introduction of 'better than perfect' healthcare technologies (Rajczi, 2008), it is unsound to imagine that weightings derived in the social and political situation of today would be reliable in the social and political situation of the future. For example, a history of the social and political acceptability of long-acting reversable contraception shows distinct changes in attitudes towards birth control before and after the introduction of the contraceptive pill (Gordon, 2019).

However, in this specific case there is no need to resolve this issue in order to produce effective research on the topic on human enhancement. The purpose of this economic model is to identify under what conditions distinct groups of outputs are produced by enhancement technologies. Therefore, it is entirely reasonable to investigate different kinds of weighting, such that – for example – we learn that certain approaches are more favourable in societies that weigh efficiency higher than equity and certain approaches are more favourable in societies that believe the reverse. It is certainly conceptually odd to treat such a key element of the output as an input to the model, but there is nothing mathematically unsound about such an approach (apart from multiplying the dimensionality of the model and generally making it harder to work with) and therefore in this very narrow case MCDA can be used without any underlying weighting criteria.

It is notable that there are some passionate advocates for MCDA in the HTA process, most notably Devlin and Sussex (2011). They argue that a move from the unitary cost-effectiveness criteria to a multi-criteria system is "inevitable", since HTA bodies already incorporate multiple criteria into their decision making processes (NICE, 2008) and therefore adopting MCDA would improve decision making without actually requiring a change of judgement. To avoid ambiguity, it is clarified here that this research assumes *no change* to existing HTA methods except those explicitly outlined by the needs of the simulation, and MCDA is used only to assess the appropriateness of each outcome in the simulation model – that is, as a proxy for the human decision-making element embedded in the HTA processes (NICE, 2013).

4.4. Methods

As with Chapter 3, the methodology for the economic model is novel and interesting but the execution of that methodology mostly uses very standard health economic approaches, for example those described in Briggs et al. (2006). This is consistent with the goals of the research as these approaches are congruent with those adopted by Health Technology Assessment agencies (e.g. NICE (2013, 2022)). Consequently, these methods are not described in detail here, as they do not significantly advance the arguments relating to better-than-perfect health. Table 6 summarises details of the parameterisation of the model, while Appendix C.1 contains full details on the methods used.

Table 6 – Summary of economic characteristics of microsimulation model

Element	**Description and justification**
Perspective on outcomes	All direct health effects, and prespecified indirect health effects (for example, Lavazza (2019)-type scenarios where enhancements for one individual can offset enhancements for another)
Perspective on costs	NHS / PSS, with scenario analysis to include all societal costs and benefits
Type of evaluation	Fully incremental cost-utility analysis within a discrete-time patient-level microsimulation model
Intervention and comparator	'Better-than-perfect' human health enhancement vs no enhancement in the same population
Time horizon	Lifetime (assumed to be 100 years)
Synthesis of evidence of health effects	Exploratory valuation of health states sourced from Systematic Literature Review in Chapter 3
Measuring and valuing health effects	Expressed in QALY
Equality considerations	Three measures of equity considered; vertical inequity as measured by Slope Index of Inequality (SII), horizontal inequity as measured by Area Under the Cumulative Concentration Curve (AUCCC), and Rawlsian

	inequity, as measured by the ratio of the least well off 10% of the intervention group compared to the least well off 10% of the control group.
Discounting	Variable between 0% and 6% for costs and benefits, which can further benefit between enhanced and unenhanced. Base case is 3.5% for both costs and benefits in both the enhanced and unenhanced state.

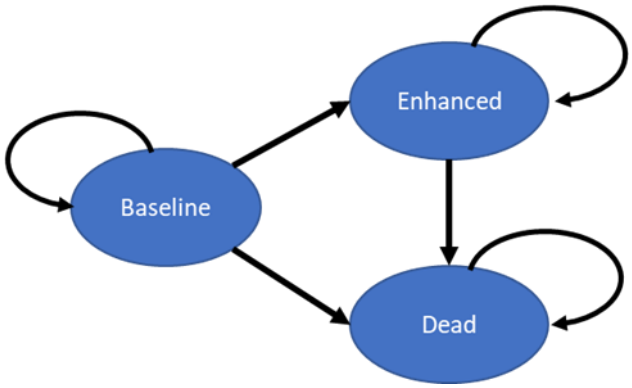
Simulations will be based on patient-level state transitions. Patients are defined at initialisation as belonging to one of up to sixteen 'archetypes', and the patient archetype defines the spread of utility at baseline, health state at baseline, transition probability, costs per health state. The archetype also determines age at baseline, and age is linked to probability of death each cycle, implemented as a hazard ratio against actuarial figures for mortality by age from the ONS (Office for National Statistics, 2021). In addition, a separate hazard ratio for mortality per health state is implemented, but set to 1 for all health states in the base case and does not vary by simulated patient. The reason why control over initial patient parameters is so complex compared to typical microsimulation models is that some of the literature in Chapter 3 hypothesises about different classes of patients receiving enhancements (for example, rich and poor people), and this method allows clear delineation between these classes. These details are summarised in Table 7.

Table 7 – Demonstration of three possible randomly simulated patients' baseline characteristics; one from 'unenhanceable' archetype 1 and two from 'enhanceable' archetype 2

	Patient 1	**Patient 2**	**Patient 3**
Archetype	1	2	2
Age	30	30	30
Initial health state	Unenhanced	Unenhanced	Enhanced
Initial cost per cycle	£500	£550	£1500
Initial QALY per cycle	0.8	0.85	1.20
Transition matrix	As per Archetype 1	As per Archetype 2	As per Archetype 2
Mortality HR	1.00	1.00	1.00

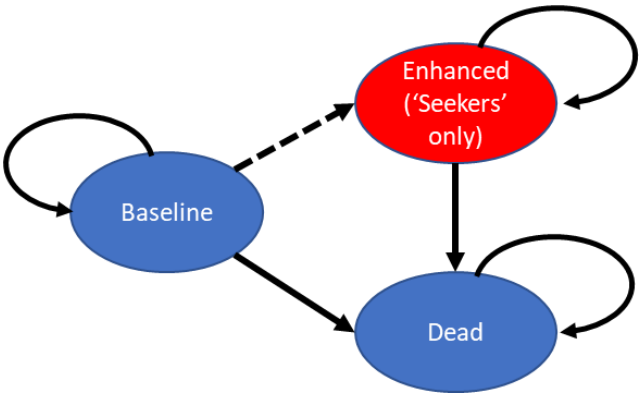
Patients in the base case of the model can exist in one of three health states; 'unenhanced', 'enhanced' and 'dead'. In the base case, patients will transition from unenhanced to enhanced and then remain in the enhanced state until death – therefore the only salient parameter is the speed at which the population enhances itself. The base case is depicted in Figure 17.

Figure 17 – State transitions matrix defined by the base case



Multiple more complex transition matrices are considered to fully explore the possible mechanisms of action that enhancements might have, based on possible models identified in Chapter 3. Some of these matrices have somewhat unusual features for a conventional health economic model, for example health states that only certain subgroups of patients can reach (Figure 18). However, these sorts of matrix are not unprecedented (see, for example, NICE NG73 (2017)) and represent the only major deviation from fully mainstream health economic methods.

Figure 18 – State transitions matrix for the 'NHS Ban' scenario, where only those patients belonging to the 'Seeker' subgroup seek out enhancements on the private market



A CHEERS statement is given in Appendix C.1.4, confirming that no major elements are missing from the discussion of the model in this thesis.

4.5. Results 1 - NHS Subversion model

Perhaps the central novel feature of this thesis is the observation that under certain circumstances enhancements can cause the NHS to become 'Subverted' and become an enhancement-only service rather than a healthcare-delivery service. Section 2.2 describes the reasons we might believe

enhancements run the risk of Subverting the NHS, and the economic model confirms that this theoretical analysis is borne out in simulations.

Figure 19 – Base Case Initialisation parameters (unchanged in subsequent outputs unless otherwise noted)

Initialisation	
Technology scenario	Standard
Posology scenario	Branded pharmaceutical
Eligible population	68,000,000
Notes	*No special notes*

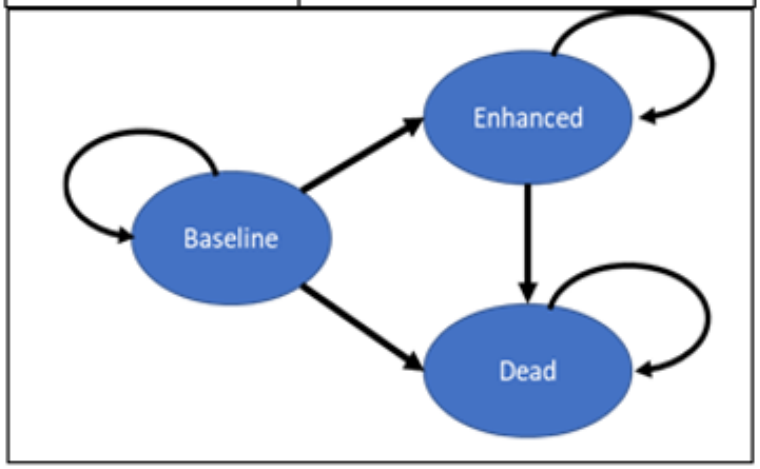


Figure 20 demonstrates that if 100% of the adult population took an enhancement which cost approximately the same as today's branded pharmaceutical products, the total impact to the NHS would be more than five times its current budget. This is clearly inconsistent with the NHS continuing to exist in its current form, and therefore a strong demonstration of the central thesis of this research; that certain human enhancement technologies create an apparently irreconcilable conflict between existing HTA methods and the continuing functioning of the NHS.

Figure 19 – Base Case Initialisation parameters (unchanged in subsequent outputs unless otherwise noted)

Initialisation	
Technology scenario	Standard
Posology scenario	Branded pharmaceutical
Eligible population	68,000,000
Notes	*No special notes*

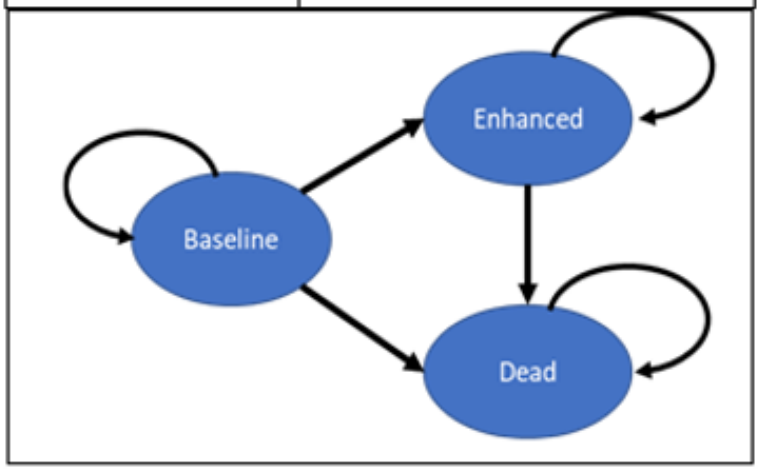


Figure 20 – Base Case Results

Results

Base case

Decision	APPROVE
ICER	£25,432

Societal case

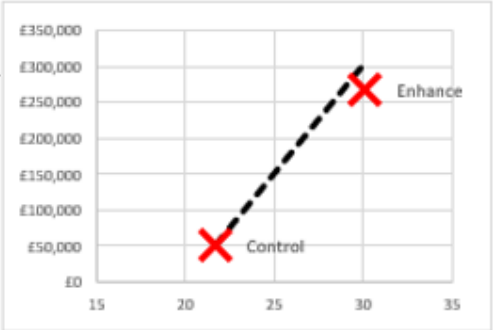
Decision	APPROVE
ICER	£25,432

Tapering case

Decision	REJECT
ICER	£35,738

Capping case

Decision	REJECT
ICER	£60,088



Equality outcomes	
NHS budget impact	522.34%
Probability harm	0.00%
Vertical equity index	0.78
H'zontal equity index	1.04
Rawlsian equity index	1.44

Due to the importance of this scenario to the central thesis of the research, scenario analysis around this point is conducted in Appendix C.2. The results of this analysis suggest the problem is particularly acute if:

- The eligible patient population is a large fraction of the total population, such that low total costs lead to high budget impacts.
- The level of enhancement offered by the treatment is large relative to the quality of life of the unenhanced state, such that a higher total cost can be supported within conventional cost-effectiveness thresholds. For example, if the enhanced state allowed for quality of life of 1.20 (i.e. the benefit was doubled relative to the unenhanced state) then the price and overall budget impact could be doubled with no change to ICER.
- The cost of the enhancement is ongoing, rather than a relatively larger up-front payment which can be amortised over multiple years (to be clear, the two treatments might cost the same amount overall, but a budget impact of 58% of the NHS' total budget each year is different to a budget impact of 58% in the first year and then a significantly smaller ongoing spend) – in the modern NHS an example of this might be the response to COVID, which cost a significant proportion of the NHS budget each month but does not invoke any novel budgetary principles since it is understood that the payment will be amortised into the future.
- The enhancement alters mortality rates then high-cost ongoing treatments combined with extended life expectancy produces very low ICERs and very high budget impact
- The cost-effectiveness of the enhancement technology is higher, such that more fundamental technologies are replaced.

The relationship between enhancements and the private market appears very similar to the relationship between conventional healthcare and the private market – specifically that a certain level of horizontal equity of health outcomes is sacrificed in order that the liberty to transact in non-harmful products is preserved. This is a tradeoff, but one which is already made by the NHS.

4.6. Results 2 – Policy positions

The central purpose of the economic model is to 'translate' bioethicists' views on how society can respond to enhancement into unambiguous mathematical code for use in health economic modelling, and thus to test whether any view is consistent with the paradigm of health economics described in

Section 2.2.2. Sections 4.6.1 to 4.6.4 below highlight important results of this process, and Appendix C gives full details on each position as background.

The term ‘translation’ is being used here metaphorically to describe expressing the ordinary-language insights of bioethicist into the mathematical language of economists. Key entities which must undergo such ‘translation’ for a successful outcome are the theorised impact of enhancements on society, the potential responses society should have towards those enhancements and the possible issues that these responses (or lack of response) could create.

It is not completely clear if a full ‘translation’ of bioethics concepts can be given in health economic terms – there may well be concepts discussed by bioethicists that do not cash out in terms health economists typically use (for example, possibly concepts of rights and obligations which are not easy to translate into consequentialist frameworks). This is not a problem specific to bioethics and health economics; Kuhn (1973) argues that almost any ‘translation’ project between disciplines is unlikely to succeed, and describes this property as ‘incommensurability of paradigms’. A famous example of incommensurable paradigms is given by Feyerabend (1993), who discusses how ‘mass’ is a term which appears in both Newtonian and relativistic physics, but in Newtonian physics mass is specifically an invariant property of an object whereas in relativistic physics it is specifically a property of an object which varies. A relativist cannot simply say to a Newtonian, “Imagine your concept of mass, but it can vary” because the concept of varying mass is untranslatable into a system where mass is absolutely fixed.

Fortunately, a one-to-one transliteration of bioethics into health economics concepts is not required in this case. The purpose of both the literature review and economic model is to thoroughly explore the enhancement strategy-space in order to assess whether there is any consistent response to the challenge enhancements might pose. As long as this objective is accomplished it doesn’t actually matter even if the bioethical insight is entirely mangled by the process of translation, since it serves its purpose by expanding the strategy space the model can consider (although, of course, I have endeavoured to give accurate ‘translations’ insofar as this is possible in order to give credit to the originator of the ideas below). A particularly important element of this is in assessing conclusions – a

bioethicist like Lavazza (2019) might argue there is an obligation to adopt some particular course of strategy and be entirely unmoved by an economist explaining that this would bankrupt the NHS – Lavazza might say, "The term 'obligation' is clearly not translating across paradigms – it means something you have to do regardless of the practical consequences", in an analogous manner to the relativist explaining to the Newtonian that 'mass' means "a thing that has to vary depending on your inertial frame of reference".

4.6.1. 'Benefit society' positions

4.6.1.1. Introduction

Section 3.4.2.1 describes how multiple authors identify that enhancements have the potential to impact wider society for good or ill (Buchanan, 2008; Outram & Racine, 2011a; Savulescu et al., 2011). The economic insight contained in these analyses is that enhancements may cause 'externalities' (both good and bad) and an assessment of health-related human enhancement should be flexible enough to handle this. Two novel policy positions are identified through the process of encoding the discussion of externalities into the economic model. A full analysis (including sensitivity analysis) of all authors associated with this position and identified in Chapter is given in Appendix C.3.

4.6.1.1. Government subsidies for prosocial enhancements

The first approach is that the government subsidise prosocial enhancements. For example, Buchanan (2008) suggests that cognitive enhancements may be so valuable in so many different domains that the government should subsidise their use even if they are not conventionally cost effective. Buchanan is an American author and so may have had in mind direct transfers to citizens in exchange for becoming enhanced, but this paradigm does not work particularly well in the context of an NHS so I assume instead the NHS are compensated by a different government department for each enhancement intervention they undertake. For example, the Department for Education might cross-subsidise intelligence enhancements to be given on the NHS.

As discussed in Chapter 3, this is effectively the same as a discount on the price of a technology (since a portion of the cost is paid for outside the NHS / PSS perspective) but implies a more direct relationship between externality benefits and non-externality costs than is currently the case. Figure

21 duplicates the economic insight driving this observation, while Figure 22 and Figure 23 show the impact of a subsidy on a hypothetical technology. The net social value of an approval does not change (because some externality value is internalised by the wider society) but a drug which is a borderline reject becomes a borderline accept under the NHS / PSS perspective.

Figure 21 – A simple conceptual model of the argument in Buchanan (2008). Red arrows represent the direction and magnitude of the subsidy.

Figure 22 – Model output for Buchanan-type subsidy scenario pre-subsidy

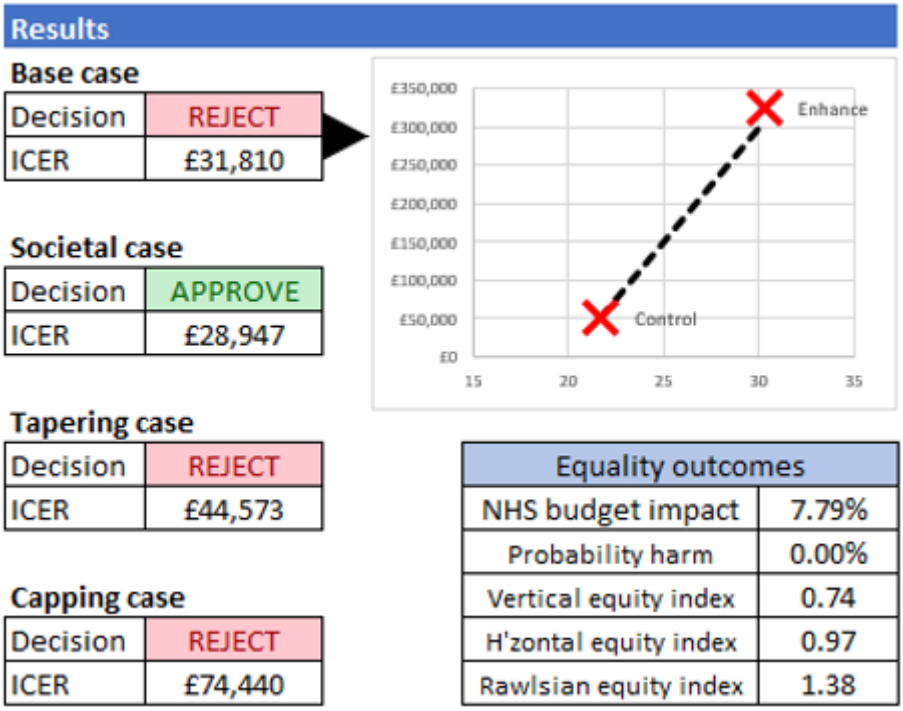
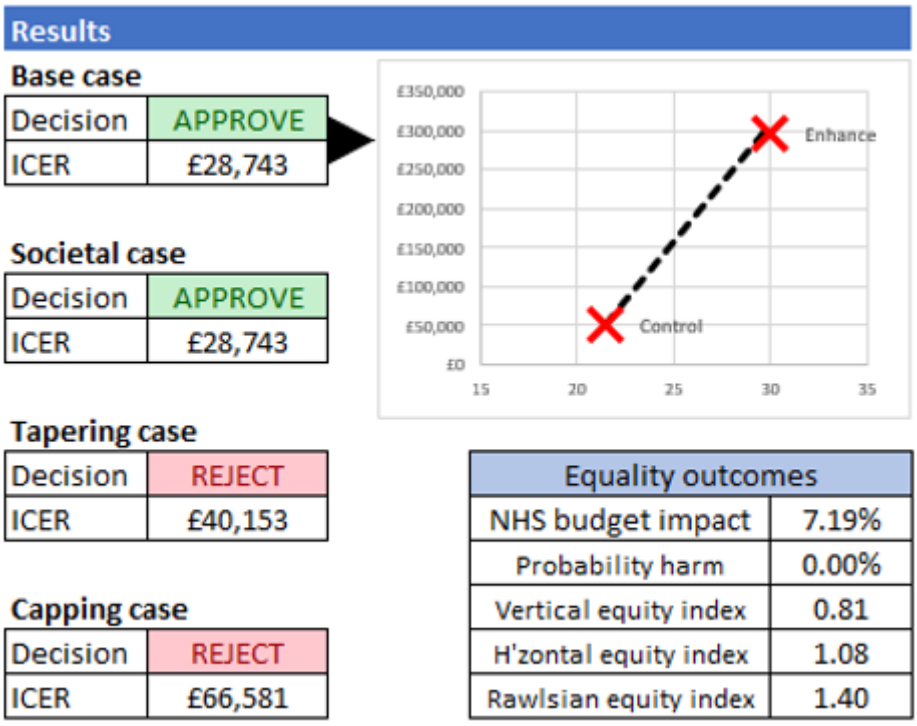


Figure 23 – Model output for Buchanan-type subsidy scenario post-subsidy



4.6.1.2. Government mandates for prosocial enhancements

The second approach is that the government mandate the use of certain enhancements (or not), which is a conclusion of multiple authors (Goodman, 2010; Lamkin, 2011; Sparrow, 2015) – although to stress not all of these authors agree government intervention would solve the problem (they appear to all agree it would at least improve it). For example, Figure 24 and Figure 25 display a scenario where society has a compelling interest in giving an enhancement (perhaps there is a compelling social interest enhancement techniques to make candidates for deep space exploration (Szocik & Braddock, 2019), but the technique is so risky and painful no individual would willingly choose to undergo it absent a government lottery / mandate). In these sorts of scenarios government intervention greatly increases overall welfare, but has a negative impact on equity as the unlucky astronauts must suffer during the enhancement (not to mention the mandate greatly imposes on the principle of bodily autonomy).

Figure 24 – Model output for Goodman-type endogeneity scenario with no government intervention

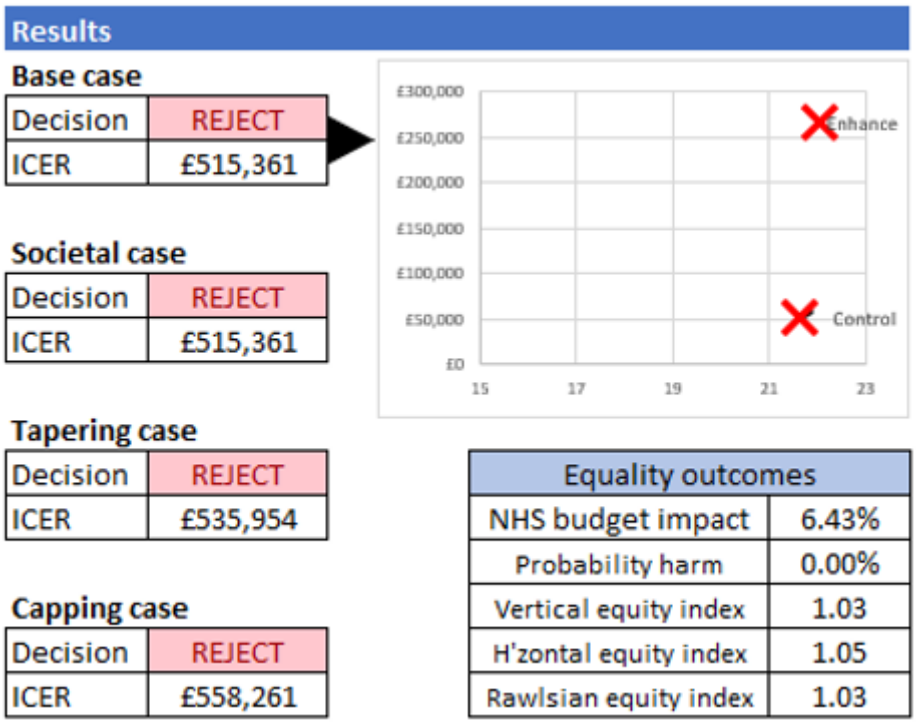
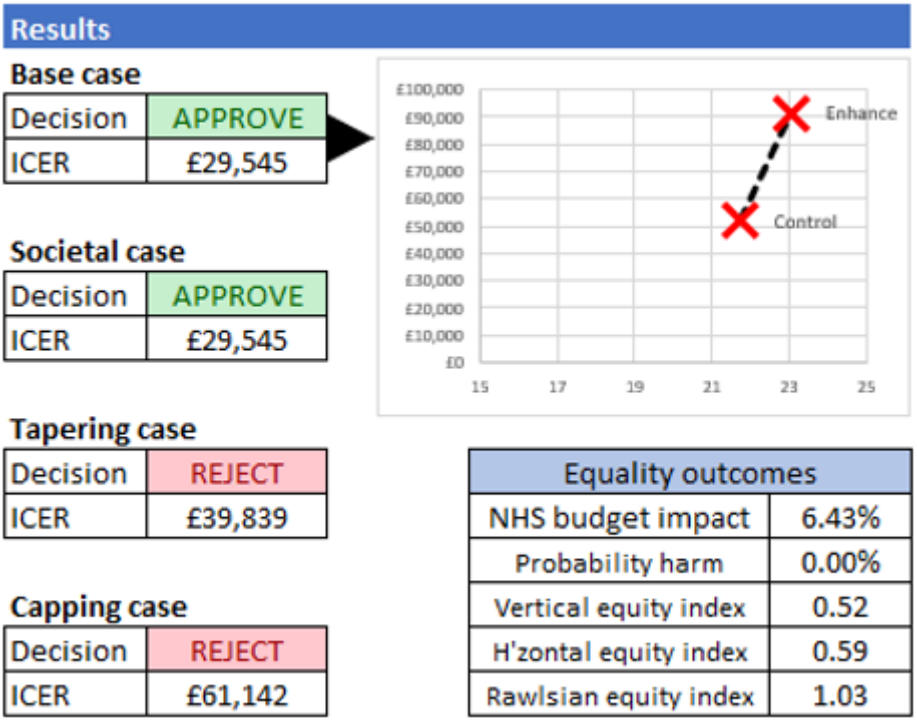


Figure 25 – Model output for Goodman-type endogeneity scenario with 20% enhancement quota enforced by government



The downsides of this scenario might be avoidable if Rajczi (2008) is correct and that there are multiple domains of flourishing which enhancement can interact with, not all of which are relevant to all people – perhaps the government can identify individuals whose personal idea of flourishing

includes exploring new frontiers of space and who therefore are more prepared to tolerate the painful enhancement procedure.

There may also be a case for government mandates controlling the number of people who enhance when the enhancement has endogeneity characteristics. That is, when the number or type of people who receive an enhancement affects how much utility it offers. This does not really have parallels in conventional medicine outside of perhaps vaccinating against infectious diseases (Adida, Dey, & Mamani, 2013), and so is considered further in a discussion of the strengths and weaknesses of the model in Section 5.6.2.

Outside of scenarios which have this endogeneity characteristic, government mandates regarding enhancements are quite similar to government subsidies if the government is perfectly accurate at targeting their mandates, and become proportionally less efficient as the government becomes proportionally less accurate.

4.6.2. Economic Disincentives Model

The Economic Disincentives Model (Dubljević, 2013a) was identified in Chapter 3 as being a particularly well-specified theory of human enhancement in terms of economic content. Unfortunately, subtle variations in the way the EDM is described between papers make a significant difference to how to encode it into the model. After considering multiple possible implementations, it was concluded that the EDM is – in health economic terms – most reasonably treated as a form of tax on enhancements and in that sense just a special case of an externality.

See Appendix C.4 for a full analysis of the position and justification for this approach.

4.6.3. ‘Restrict society’ positions

An obvious corollary of mandating the use of pro-social enhancements is banning the use of anti-social enhancements. This is a position discussed (although not always endorsed) by multiple authors (Dubljevic, 2012b; Rajczi, 2008; Sparrow, 2015) and dealt with extensively in the context of sports doping in the wider human enhancement literature (for example Loland (2011), but the literature is very broad). Chapter 2 identifies that the prospect of banning enhancements is challenging due to the difficulty of drawing a clear line between ‘therapy’ and ‘enhancement’ (Boorse, 1975). Nevertheless,

HTA agencies have a huge advantage over the complex philosophical considerations of bioethicists cited in Chapter 2, since they can arbitrarily define any quality of life >1 as being 'enhancement' and therefore directly target 'better than perfect' health rather than enhancement *per se*.

4.6.3.1. Full bans

The purpose of a ban is to prevent any bad effects of enhancements from reaching society – this certainly does include the effect of NHS Subversion, but more realistically includes the concerns of bio-conservatives around – for example – the impact of enhancements on economic liberties (Sparrow, 2015) or autonomy more generally (Buyx, 2008). From an HTA perspective, a particularly challenging element of a ban is one where patients with a disease have the option of a technology which not only cures their disease but also enhances them, and are therefore denied access to this technology by a blanket ban on enhancements. Although it seems unlikely that we would invent an enhancement but no cure, this sort of technological 'leapfrogging' is not unprecedented (Fudenberg, Gilbert, Stiglitz, & Tirole, 1983), and the characteristics of enhancement technologies make it reasonably plausible to believe – it would nowadays be more difficult and expensive to build a bookcase by hand than to buy a higher-quality bookcase from Ikea; insofar as the state had an interest in providing bookshelves it would prefer the lower-cost and higher-quality Ikea option. Similarly, if the enhancement technology was biomechanical or based on information technology in some respect, we might imagine it would be more expensive to downgrade to an unsupported version of the technology, and the moral case for doing so would be uncertain – so it is not that a non-enhancing version of the technology cannot be produced, it is that it is not a discrete alternative to the enhancing technology.

Nevertheless, a blanket ban is potentially a sensible response in a few situations – Figure 26 shows an approvable technology with some significant externality downsides and Figure 27 shows a situation where an approvable technology has catastrophic equity implications. In both of these cases a blanket ban may be a more sensible policy choice than arguing with the special interest groups who benefit from the enhancement every single time, depending on how often enhancement technologies tend to have these characteristics. Nevertheless, this seems to be an argument lacking ambition – it would be

far better to state a principled position for when society should value enhancements ahead of therapy and when the opposite should be true.

Figure 26 – Model output for approvable technology with significant externality downsides

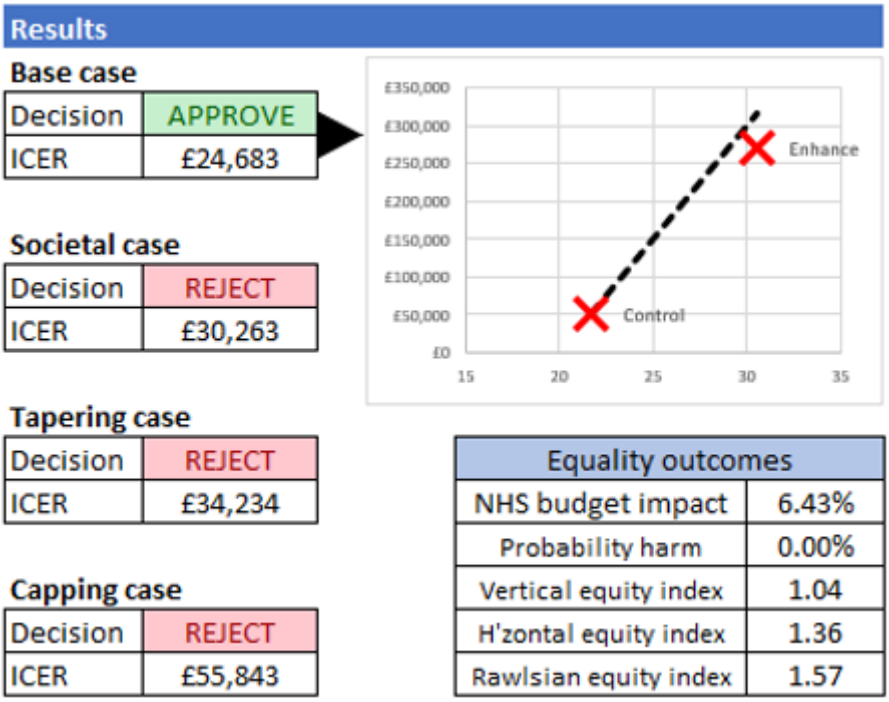
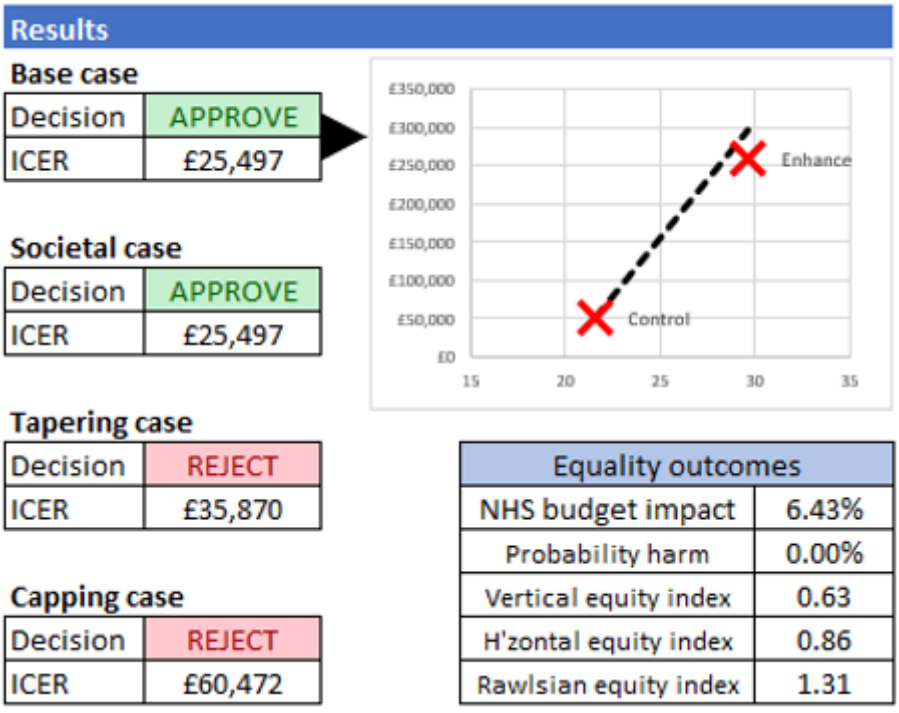


Figure 27 – Model output for approvable technology with significant inequity downsides



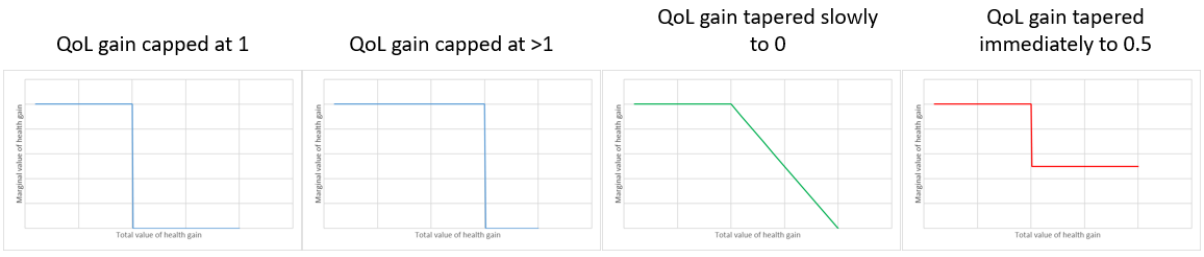
4.6.3.2. *Partial bans*

One such principled approach would be to come up with some definition of what a technology is 'principally' used for (i.e. treatment or enhancement) and ban those therapies which were principally being used for enhancement (an example might be that the female contraceptive pill was originally prescribed under these conditions – that is, as a treatment for period pain which coincidentally allowed control of fertility (Dhont, 2010)). This is consistent with theories of healthcare which emphasise the role of healthcare as being to give everyone a 'fair innings' at life and appears to be the implicit recommendation of some authors who did not have explicit economic insights to be picked up by the review (e.g. Sandel (2012)). However – notwithstanding the philosophical issues with identifying the ''principal'' use of a technology – the downside is that it too fails to correctly identify when society genuinely does value enhancement ahead of conventional therapy.

4.6.3.3. *Additional hurdles*

An alternative to an outright ban is to force enhancements to clear an additional hurdle to be considered cost-effective. What exactly that hurdle should be is a matter of empirical ethics (that is, what hurdle corresponds most closely to the sort of world the society would prefer) but might look like one of the schema shown in Figure 28. It is interesting that the new NICE methods (NICE, 2022) have considered this problem from the opposite end (that is, how can we pay more for treatments which are particularly important) and settled on something resembling the fourth 'tapering' option – this suggests there is institutional acceptance of this sort of approach at HTA agencies.

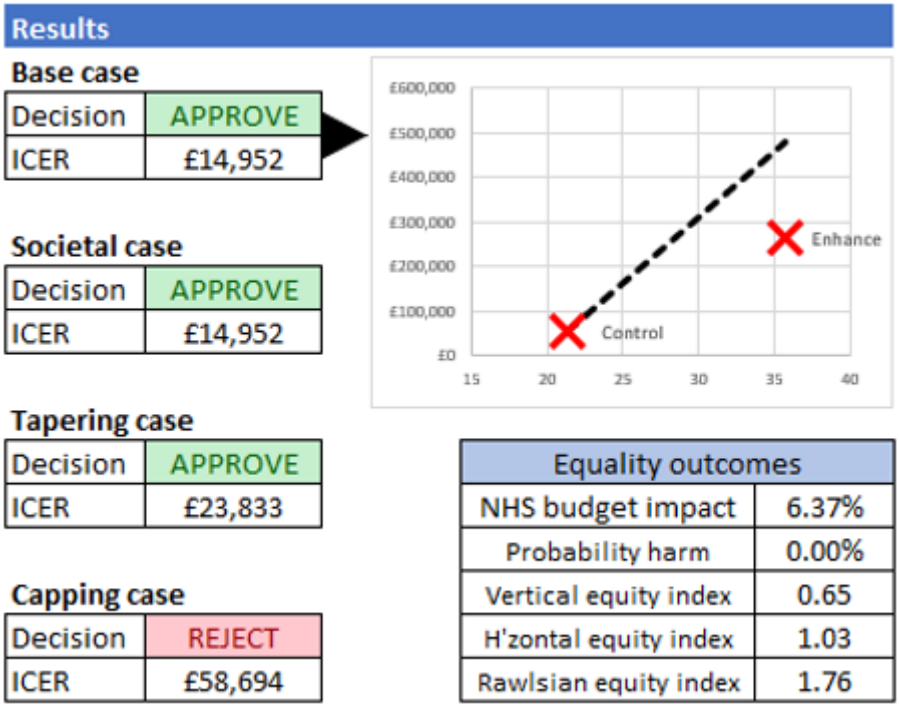
Figure 28 – Schema showing some variations of restriction approach



Depending on the details of the implementation, all of these restriction approaches have the attractive quality of being able to consistently provide enhancements society desires while setting a limit on how far away the NHS can drift from being a 'therapy' organisation. The main difference between

'capped' and 'tapered' approaches are that the 'capped' approaches guarantee that only a certain proportion of the NHS budget can be spent on any individual enhancement, whereas 'tapered' approaches could in principle still lead to NHS Subversion if a sufficiently attractive enhancement was created (for example see Figure 29), but that this enhancement would have to be sufficiently good that the public agree that it is worth the NHS becoming Subverted to provide it, so this may not be as problematic as it appears.

Figure 29 – Model output showing a difference between 'capping' and 'tapering' case



At the margin, restrictions (and some bans) raise the possibility of patients engaging in moral hazard behaviours (patients doing unwanted things because the incentive structure encourages it – see for example Finkelstein (2014). For example, if the NHS makes bionic legs available only to those with conventional diseases affecting their leg, then if bionic legs are sufficiently attractive it may be economically rational to attempt to damage your biological leg in order to gain access to the enhanced upgrade. Beyond the margin this behaviour matters less, although if a series of low-cost low-impact enhancements are created which affect multiple domains of health then the 'margin' for each of these domains may be quite extensive.

4.6.4. ‘Distributive justice’ positions

4.6.4.1. Introduction

Multiple authors note that enhancements have the potential to radically alter the existing relationship between equity and efficiency tradeoffs in healthcare (Allen & Strand, 2015; Kim et al., 2019; Lavazza, 2019; Lin & Allhoff, 2008; Ray, 2016). Therefore, these authors argue, enhancements which are cost-effective should have to clear another bar based on improving equity of health outcomes, for some measure of ‘equity’ (in the model I assume horizontal, vertical and Rawlsian equity cover enough of the territory for the purpose of this investigation, but it should be acknowledged there are other definitions of ‘equity of health outcomes’ which might be affected by enhancement). These suggest HTA approaches built around this radical new opportunity rather than attempting to ‘patch flaws’ in existing HTA methods.

Two enhancements specific HTA approaches are suggested by the literature. Ray (2016) suggests that those who are *ex ante* disadvantaged receive enhancement to compensate them for this disadvantage and render *ex post* inequity as close to zero as possible – addressing vertical and horizontal inequality, while Lavazza (2019) suggests that the inequity arising from the fact that some may be able to enhance and some cannot should be regarded as illegitimate and those individuals who cannot or do not want to enhance should be compensated.

4.6.4.2. Compensate those who cannot enhance

Lavazza (2019)’s argument proposes that those who cannot or do not wish to enhance could be compensated the value of this enhancement. This interacts very badly with precepts of health economic analysis under budget constraints, since it fails to solve any of the identified problems with enhancement (such as Subversion) but increases the cost of Subverting technologies massively. Nevertheless, Lavazza is right that if this is a bullet we are prepared to bite then we can achieve a population which is net healthier than before enhancements but where inequity of health outcomes is effectively zero.

Figure 30 – Model output showing a technology which would be approvable except for compensating the unenhanceable to achieve near-zero health inequity

Results

Base case

Decision	REJECT
ICER	£50,186

Societal case

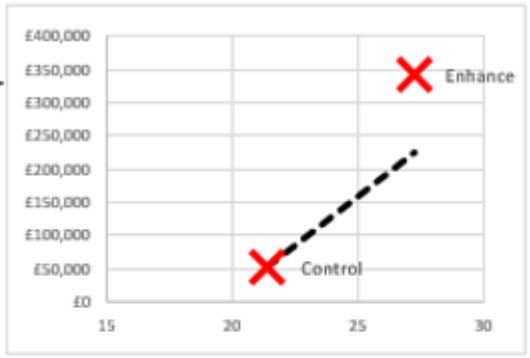
Decision	REJECT
ICER	£50,186

Tapering case

Decision	REJECT
ICER	£65,618

Capping case

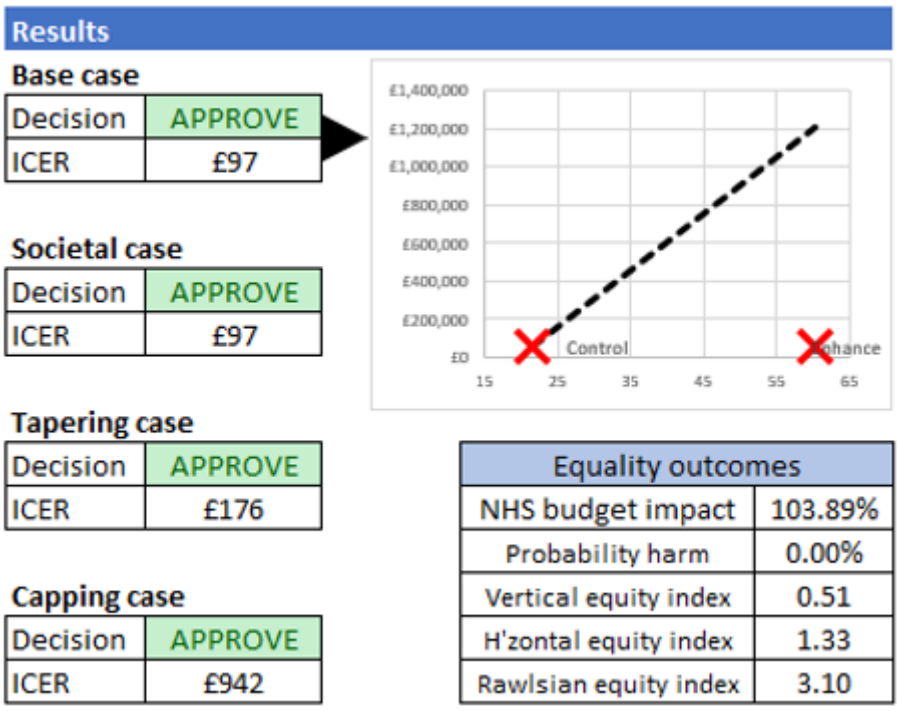
Decision	REJECT
ICER	£94,753



Equality outcomes	
NHS budget impact	8.38%
Probability harm	0.00%
Vertical equity index	1.04
H'zontal equity index	1.01
Rawlsian equity index	1.15

An interesting interaction occurs when considering enhancements which offer extreme value to society. While Lavazza does not specify who determines the level of compensation due to the unenhanceable, one might consider society's valuation on being enhanced in that way to be a good proxy, especially in the absence of externalities (which is to say, the ICER threshold (Wagstaff, 1991)). However, the threshold moves in response to the treatments available at the margin, which in the case of highly effective enhancements means that the cost per QALY might be <£100 when the NHS budget is completely exhausted (see Figure 31). Therefore, as the value of enhancement increases, the value per QALY society assigns enhancement will shrink, and Lavazza's position will become self-defeating unless a different HTA approach is adopted.

Figure 31 – Model output for threshold-altering case



4.6.4.3. Treat enhancement as an unearned / illegitimate advantage

Ray (2016)'s argument initially appears more consistent when faced with Subverting enhancements. Since enhancing the healthy at the cost of the sick raises inequity, there is a limit on how far enhancements can be bought at the expense of more conventional therapy. However, under certain circumstances Ray's argument does little to defeat the general objection of Chapter 2 that enhancements can Subvert the NHS – if health is made up of only two factors (mobility and pain, for example) then it would be possible for an enhancement of the mobility domain to level up all individuals while preserving their rank order on the pain dimension, and so keep the overall level of inequity the same (or even reduce it) while subverting the NHS-as-pain service into an enhancement-only service. Therefore, Ray's argument does defeat the problem of NHS Subversion, but only under a specific set of criteria for the enhancement technologies - Figure 32 demonstrates an extreme-value failure case for the argument.

Figure 32 – Model output for a Ray (2016) defeating enhancement, where horizontal inequity is unchanged but enormous vertical inequity is created through the variation of different domains

Results

Base case

Decision	APPROVE
ICER	£1,137

Societal case

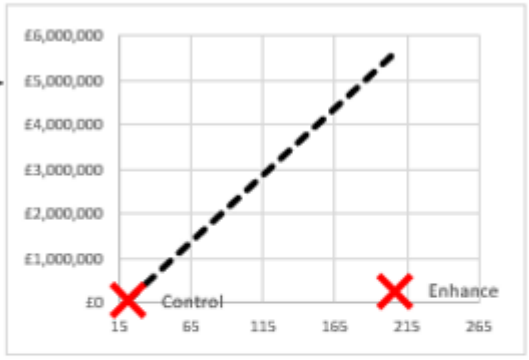
Decision	APPROVE
ICER	£1,137

Tapering case

Decision	APPROVE
ICER	£2,234

Capping case

Decision	REJECT
ICER	£62,878



Equality outcomes	
NHS budget impact	6.43%
Probability harm	0.00%
Vertical equity index	0.10
H'zontal equity index	0.97
Rawlsian equity index	9.47

Furthermore, a logical extension of this argument is that harmful enhancements might be offered to or forced on otherwise healthy individuals in order to lower their overall health and thus 'level down' the target level of health inequity (Parfit, 1984). See Figure 33 for a demonstration of this in the economic model.

Figure 33 – Model output for a 'levelling down' case where healthy individuals are given an anti-enhancement to bring them down to the levels of sick individuals

Results

Base case

Decision	REJECT
ICER	DOMINATED

Societal case

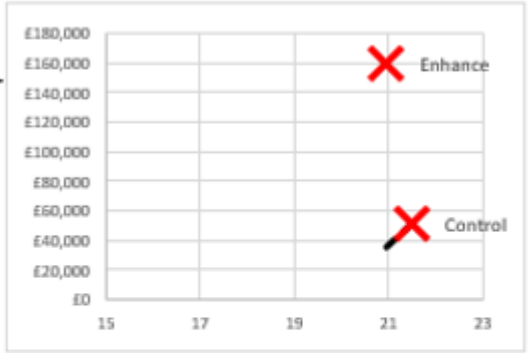
Decision	REJECT
ICER	DOMINATED

Tapering case

Decision	REJECT
ICER	DOMINATED

Capping case

Decision	REJECT
ICER	DOMINATED



Equality outcomes	
NHS budget impact	6.43%
Probability harm	97.00%
Vertical equity index	0.99
H'zontal equity index	0.99
Rawlsian equity index	1.05

The literature on 'levelling down' is extensive and technical, but in a health economics context there appears to be agreement that it must be mistaken to accept the 'levelling down' conclusion – if we cannot cure cancer the 'levelling down' principle seems to require that we give everyone cancer, and this would seem to be a fundamentally misguided notion of what the NHS is for (Savulescu & Cameron, 2020). Whether 'levelling down' can actually be avoided in a system which mathematically optimises for a given level of inequity is difficult to identify without seeing details of exactly how the process might work. It would not, for example, be possible to avoid the levelling down objection by stipulating that harmful treatments never be given because that would rule out existing south-west quadrant technologies (Dowie, 2004). The general issue of 'levelling down' and HTA is beyond the scope of this research, other than to note that Ray's proposal creates an issue here where none exists in conventional HTA.

4.7. Conclusions

Methods of theory generation in economics are well established (Varian, 1992), but would work imperfectly for this research for a variety of reasons. Consequently it is necessary to adopt a simulation model in order to 'build theory' (Dekkers et al., 2020) and allow for the possibility of unexpected or emergent results to take the research in a different direction. Although the consensus in

the economics literature is that simulation models are typically not well regarded (Lehtinen & Kuorikoski, 2007), specific features of this research mean that the typical objections do not apply; in fact simulation modelling is the tool of choice for considering artificial societies (Gilbert & Conte, 1995) and has been successfully used in artificial societies with enhancement-like characteristics (Doran, 1997).

To accomplish the goals of the research, the economic model is created with the purpose of being as similar as possible to conventional HTA assessment models, with the aim of 'translating' the bioethics theories from Chapter 3 into health economic concepts. This is accomplished with a microsimulation model substantially based on conventional health economic literature (Briggs et al., 2006). The only major deviation is the deliberate use of Multiple Criteria Decision Analysis to help aid the 'translation' of ethical / extra-welfarist concepts.

A key finding of the economic model is that the concept of NHS Subversion described in Section 2.2 can be replicated inside a conventional HTA submission model, indicating that it is more than a theoretical worry for HTA agencies. A novel finding the economic model adds is that the scope of Subverting technologies is much greater than one might perhaps expect from reading Section 2.2; the sensitivity analysis conducted in Appendix C.2 shows that almost any 'better-than-perfect health' - type enhancement can Subvert, but that certain characteristics of the enhancement can make the problem more or less acute, suggesting an obvious focus for NHS horizon scanning observatories studying the problem.

A second key finding of the economic model is that many bioethics recommendations from Chapter 3 can be 'translated' into health economic language and so included in an economic model. Section 4.6 reaffirms that the major work in this area coheres around two areas (improving efficiency and altering the existing equity / efficiency tradeoff space), but the use of an economic model to map this space productively led to two new avenues of policy generation; inverting existing theories and discovering new theories *de novo* from opportunistic use of the economic model. Table 8 summarises the positions identified in this process.

Table 8 – Summary of theories of health-related human enhancement

Approach	Description	Source
1.1	Conventional HTA process (NHS / PSS perspective)	Briggs et al. (2006)
1.2	NHS stops existing and converts to US-style HMO-led market	Possible variation of 1.1
1.3	Mixed-market system	Possible variation of 1.1
2.1	Conventional HTA process (societal perspective)	Briggs et al. (2006)
2.2	Societal perspective plus government subsidy for prosocial enhancement	Buchanan (2008)
2.3	Societal perspective plus government mandate for prosocial enhancement	Goodman (2010)
3.1	Economic Disincentives Model	Dubljević (2013a)
4.1	Ban on all technology which could potentially enhance	Inversion of Goodman (2010)
4.2	Ban on all technology used principally to enhance	Possible variation of 4.1
4.3	Heavily disincentivise enhancement with 'cap' on QoL > 1	NICE (2022)
4.4	Heavily disincentivise enhancement with a 'taper' on QoL > 1	Possible variation of 4.3
5.1	Attempt to minimise inequity	Ray (2016)
5.2	Compensate those who cannot / do not wish to be enhanced	Lavazza (2019)

Perhaps more generally, the most important finding of the Chapter is that the economic model – presented as Supplementary Material – is capable of encoding a wide variety of bioethics positions on human enhancement. This is a valuable finding from the perspective of interdisciplinary dialogue between bioethicists and health economists, and also a valuable finding from the perspective of this thesis; it allows for a more exhaustive search of the health economic enhancement space in Chapter 5, and therefore for robust conclusions to be drawn across the entire thesis.

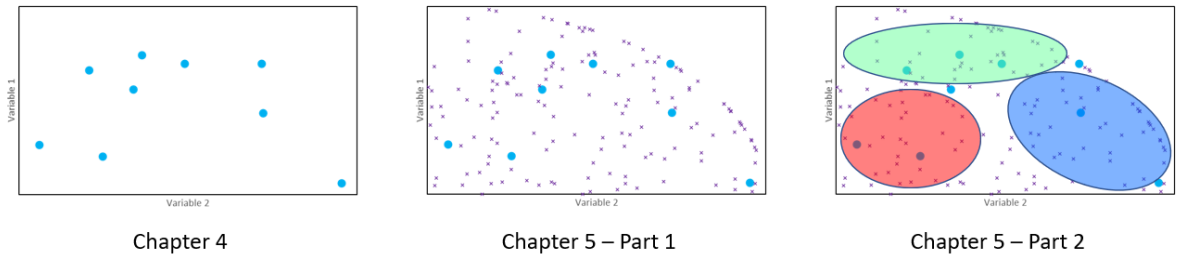
Chapter 5. Developing a health economic theory of human enhancement

5.1. Chapter Summary

This Chapter further explores the economic model from Chapter 4, and uses the results of this exploration as the basis to form a preliminary economic theory of human enhancement.

Figure 34 demonstrates how the Chapter will proceed, conceptually. By using the literature review (Chapter 3) we can identify and 'translate' a number of bioethics arguments into cost-effectiveness terms (Chapter 4). By randomly varying structural assumptions and parameters of these arguments, it is possible to map the whole health economics relevant enhancement space. This space can then be reduced using conventional dimensionality / complexity reduction techniques such that the entire space can be described using only a few terms.

Figure 34 – Conceptual model of how Chapter 5 builds on Chapter 4 to develop a theory of enhancement



As may be clear from the above, it impossible by design for the research to identify a 'best' health economic theory of human enhancement, since different people will have competing conceptions of the good, and specifically where the good lies on the tradeoff framework established by the model. It will only be possible to identify theories which are the best at maximising some particular distribution of values, and possibly to identify a productivity frontier in some cases. However, the goal of the research is not to identify what the 'best' theory of enhancement is, but rather whether any such theory exists in a consistent fashion. Consequently, the design of the research is reasonable for the goal identified.

5.2. Probabilistic sensitivity analysis

Probabilistic Sensitivity Analysis (PSA) was undertaken on the economic model using conventional techniques as described in Briggs et al. (2006). It was found that 1000 iterations of the model offered the best balance between speed and convergence (see Appendix D.1.2). Some examples of randomised input and output data from this process are given in Appendix D.1.3.

Best practice in data-driven research is to summarise and visually inspect data before beginning any form of analysis (Severance, 2016). This is done via tabulation in Table 9 and graphically in Figure 35, again presented in line with entirely conventional health economic techniques (Briggs et al., 2006). The conventional methods notwithstanding, it is worth noting that some of these results are entirely ridiculous by the standards of the technologies HTAs are designed to assess – for example Figure 35 shows outlying results where an individual gains near 80 QALY for enhancement. This is expected behaviour of the model and supports a key argument of this research, which is that policy makers have not fully understood the magnitude of change that enhancements could bring to conventional HTA.

Further information on PSA is given in Appendix D.1 as background information.

Table 9 – Summary data regarding PSA outcomes

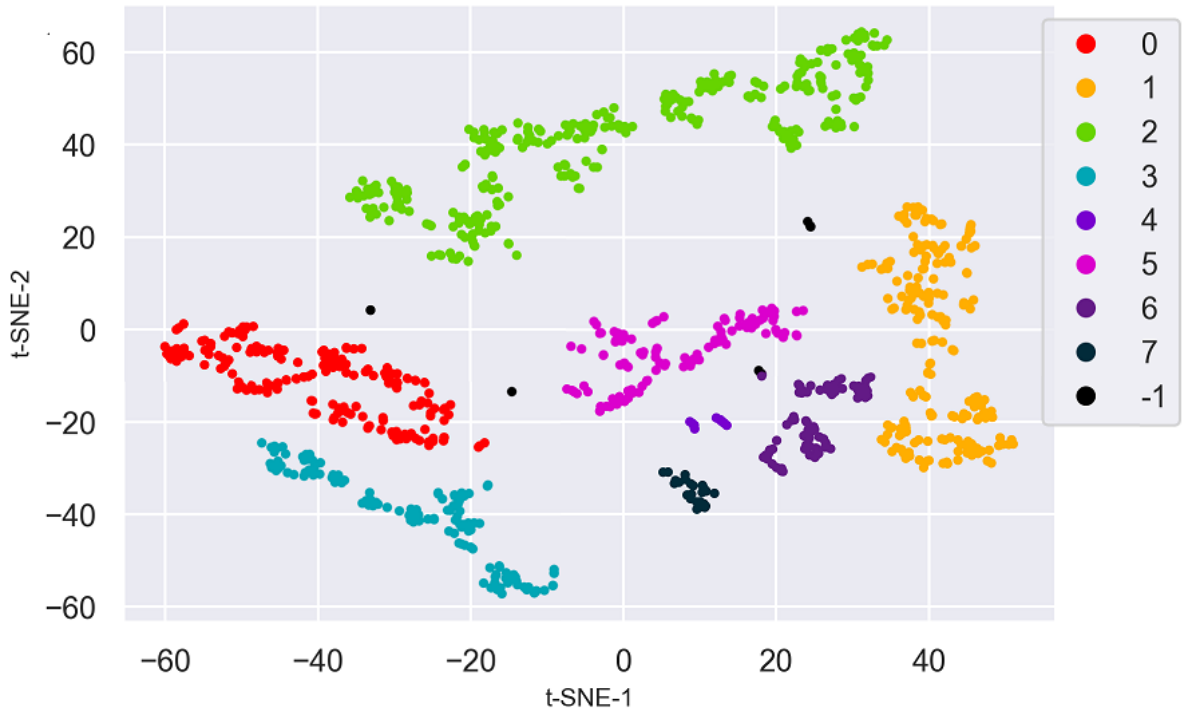
	Mean value	**Distribution (St Dev)**
Total iterations	1000	
Probability ICER <£30,000	0.71	0.02
Average NHS budget impact in peak year	0.13	0.22
Mean delta spend per patient	£86,022	£157,229
Mean delta QALY per patient	6.85	15.25
Implied ICER	£12,558	N/A
Mean Net Monetary Benefit (NMB)	£119,339	£476,114
Probability of a meaningful (>12) QALY increase	0.26	0.05
Probability of harming a patient by enhancing them	0.23	0.35
Probability of enhancement being dominated	0.17	0.07
Probability of enhancement dominating	0.21	0.06

Figure 35 – Summary PSA probability cloud

A more modern method of visualisation is demonstrated in Figure 36, where the data are presented using a dimensionality reduction technique known as t-Distributed Stochastic Neighbour Embedding (t-SNE) to convert the multiple dimensions of the decision analysis criteria into a 2D model of the searched space (Van der Maaten & Hinton, 2008). Figure 36 shows that approximately six or seven main clusters appear when the t-SNE technique is used, which is a useful prior for the subsequent dimensionality reduction work conducted in Section 5.5.

Further information on the t-SNE is included in Appendix D.2 as background information.

Figure 36 – Summary t-SNE graph for Clustering Model



5.3. Clustering algorithm methodology

While dimensionality reduction techniques like t-SNE certainly improves over naïve data visualisations like those in Figure 35, it is difficult to give any interpretation to these outputs beyond general statements of the obvious, such as that the search space spans a highly heterogenous population. This is because in making the data comprehensible to humans the algorithm must necessarily redundantly encode (or discard) some of that data (Treshansky & McGraw, 2001), making it almost impossible to analyse on a deep level. Rather than losing the data we have spent all of Chapter 4 generating, it would be significantly better to have a machine learning technique identify 'clusters' of interesting behaviour in the rich multidimensional space where they actually occur, and then flag these 'clusters' to the end-stage analyst.

The problem of 'clustering' has been described in the literature since the early 20th Century (Fisher, 1936), and simple early approaches have proved to be robust tools for solving this sort of problem (even modern approaches are sometimes outperformed by a naïve Bayesian model (Binder, 1981)). However, recent advances in machine learning have made the technique applicable to a wide range of problems, including the specific statistical problem of this research (Treshansky & McGraw, 2001).

In general, there is no single 'best' algorithm (Michie, Spiegelhalter, & Taylor, 1994), and the algorithm which should be used depends on the dataset. This notwithstanding, it is agreed in the literature that certain simple heuristics can provide a good guide to the most appropriate algorithm to use in most cases (Brodley, 1993). A simple set of heuristics is given in Li (2020). Their taxonomy varies depending on whether the techniques are supervised or not (in layperson's terms meaning whether the model is shown examples of each kind of category before it begins its own categorisation approach (Russell & Norvig, 2002)), the broad technique used to classify the clusters and then within each technique a series of additional questions to narrow down the approach further, particularly whether the data are structured into hierarchies and whether the output must necessarily be probabilistic. With respect to this research:

- As there is no significant corpus of examples of enhancement technologies being assessed by NICE, an unsupervised approach is required.
- The purpose of the algorithmic assessment is to reduce the complexity of the search space (Treshansky & McGraw, 2001). In principle, dimensionality reduction techniques such as Principle Component Analysis might be an interesting approach to take (and such techniques have been used in healthcare in this fashion, e.g. Wood, Simmatis, Boyd, Scott, and Jacobson (2018)). However, dimensionality reduction is probably less helpful in this case than clustering, as the problem is not so much representing the complexity of the data in lower-dimensional space as identifying the sorts of decisions that might have to be taken in the future. Therefore, dimensionality reduction appears to require two steps to what clustering can do in one, and is more suitable for anyway.
- The output from the model will not be hierarchical, and therefore hierarchical models are inappropriate (Barto & Mahadevan, 2003).
- Finally, probabilistic assignment to clusters is not relevant, so these techniques add complexity for no gain.

Table 10 summarises these approaches, and applies colour coding to indicate whether each parameter would be appropriate for this research against each algorithm type.

Table 10 – Summary of machine learning approaches, taken from Li (2020)

Algorithm	Supervised?	Technique	Hierarchical?	Probabilistic?	Need to specify k?
DBSCAN	No	Clustering	No	No	No
k-Nearest Neighbour	No	Clustering	No	No	Yes
k-mean	No	Clustering	No	Yes	Yes
Gaussian mixture model	No	Clustering	No	Yes	Yes
Hierarchical	No	Clustering	Yes	No	No
Principle Component Analysis	No	Dimensionality	N/A	N/A	N/A
Singular Valve Decomposition	No	Dimensionality	N/A	N/A	N/A
Latent Dirichlet Analysis	No	Dimensionality	N/A	N/A	N/A
Linear Regression	Yes	Regression	N/A	N/A	N/A
Decision Tree	Yes	Regression	N/A	N/A	N/A
Random Forest	Yes	Regression	N/A	N/A	N/A
Neural Network	Yes	Regression	N/A	N/A	N/A
Gradient Boosting Tree	Yes	Regression	N/A	N/A	N/A
Naive Bayes	Yes	Classification	N/A	N/A	N/A
Logistic Regression	Yes	Classification	N/A	N/A	N/A
Linear SVM	Yes	Classification	N/A	N/A	N/A

Potentially appropriate Complex / see discussion Likely inappropriate

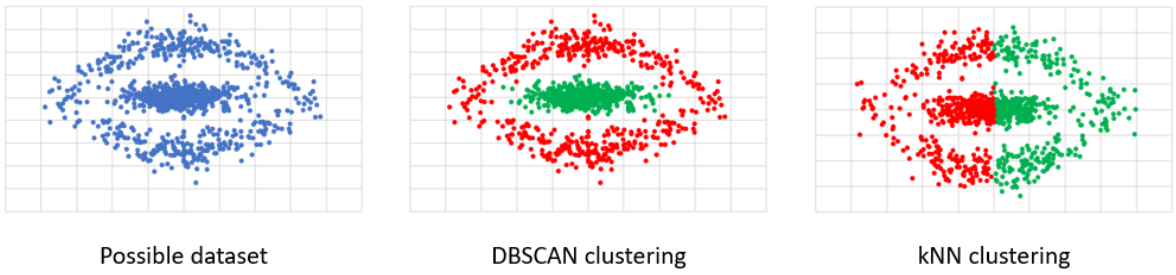
Based on these considerations, Density-Based Spatial Clustering of Applications with Noise (DBSCAN) or k-Nearest Neighbour (kNN) would appear to be the most appropriate option. K-mean and Gaussian mixture models could be used but are inferior to kNN in that they are more complex for no gain of output (probabilistic assignment to a cluster is irrelevant for our purposes).

The principal difference between kNN and DBSCAN is that kNN requires k to be specified whereas DBSCAN does not (k refers to the number of clusters that the results will be divided into). Clearly it is not actually possible to specify k in the conventional sense, since prior to running the model we have no idea how many kinds of enhancement-related HTA decisions there could be. This would heavily recommend models which are initially agnostic to the value of k, like DBSCAN. However, as the purpose of the model is to offer economic insight into the kinds of decisions that might face health technology appraisal bodies, too many clusters would defeat the point of the exercise – one cannot meaningfully say anything insightful about thousands of unique clusters. Therefore, it might be better

to restrict the data to the best fit which reasonably serves this objective, for example imposing a restriction that k<10 and gradually increasing k until a good fit is found. Exploratory modelling used a kNN approach and was able to identify meaningful clusters at k-levels between 2 and 5, so there is some empirical support for this approach.

A second key difference between the approaches is that DBSCAN can gracefully handle nonlinearity in the data whereas kNN cannot (Schubert, Sander, Ester, Kriegel, & Xu, 2017). Figure 37 demonstrates a characteristic way in which kNN will fail to characterise nonlinear clusters. It would be extremely surprising to find nonlinear results like Figure 37 in the actual data, since all inputs are linear. Nevertheless one critical theoretical feature of simulation models is the ability to demonstrate 'emergence', which is to say more complex behaviours arising from the interaction between simple behaviours (Gilbert & Troitzsch, 2005). The loss of the ability to identify nonlinearity in results would be disappointing, as correctly classifying emergent behaviours is one of the key arguments for adopting the simulation approach rather than the more conventional computational approach. Nevertheless, not all emergent behaviours are nonlinear and not all nonlinearities are incorrectly classified by kNN (Schubert et al., 2017), so whereas the decision regarding specifying k is absolutely fundamental to the choice of method, decisions around nonlinearity could make no difference in practice.

Figure 37 – Example of kNN failing to identify an obvious cluster due to nonlinearity



On balance, kNN appears preferable for logistical reasons; if DBSCAN identified too many clusters it would fail to assist the research at all because the problem set would not have been reduced enough to be helpful, whereas if kNN fails to identify a nonlinear cluster the research will still be helpful (albeit lacking precision). A final logistical point is that DBSCAN is very inefficient to run in Excel's

architecture whereas kNN is not – clustering 1000 datapoints in Excel takes approximately 7000 units of time with kNN but approximately 1,000,000 units of time with DBSCAN (Schubert et al., 2017). Consequently, implementing DBSCAN would require unconventional model architecture, whereas kNN can be implement in Excel alongside the main model.

It should be noted that a weakness of the methodology here is that a known superior method exists to either kNN or DBSCAN in isolation – specifically, using both algorithms (Gama & Brazdil, 1995) (or ideally running all possible clustering algorithms) and selecting the best fit (Brazdil, Gama, & Henery, 1994). The justification for not doing this is that the accuracy of classification is not precisely what we are interested in in the Clustering Model – merely the reduction of the search space to something human-tractable. Therefore, a simple and fast method to get most of the way to perfect results is superior to a complex method in this instance.

Note, incidentally, that the kind of machine learning described in Table 5 is supervised whereas clustering algorithms are unsupervised. Therefore, there is no overlap with this Section and the choice of simulation model in Section 4.3.1, except insofar as both techniques can broadly be described as 'artificial intelligence'. This is somewhat important, as ideally theory and methodology should be congruent and without this clarification it may appear that they are not.

5.4. Clustering algorithm methods

Several implementations of kNN are described in the literature (Cunningham & Delany, 2020) but no implementation was described specifically to Microsoft Excel and therefore the code was hand-written (i.e. not following any specific reference other than the general mathematical references described above). Beyond this, the implementation of the kNN was entirely standard, and details are given in Appendix D.3 for background.

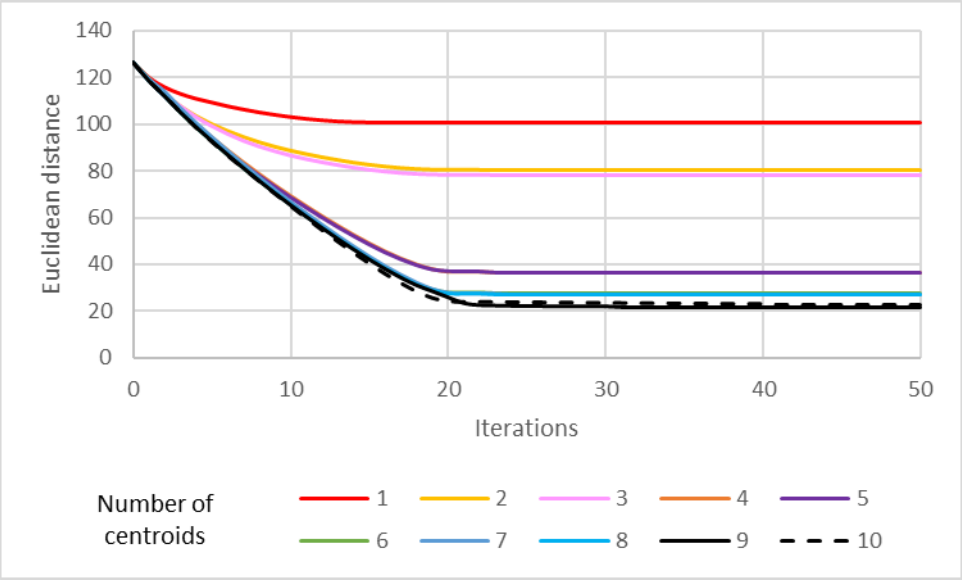
5.5. Clustering algorithm results

5.5.1. Parameterising k

The optimal number of centroids (k) cannot be known prior to examining the data, and therefore parameterising k for the algorithm is the first result described. Since increasing the number of clusters and increasing the runtime of the algorithm make the analysis more computationally complex and

risks overfitting, the goal is to select the least number of centroids which give adequate results in a tractable length of time. Figure 38 demonstrates the rate at which adding centroids and allowing the clustering algorithm to run for longer can improve the overall accuracy of the algorithm, based on a training dataset of 10% of the full PSA run. Details of the implementation of kNN are given in Appendix D.3.

Figure 38 – Improvement in accuracy by increasing number of centroids and number of gradient boosting iterations



Overall, it would appear that there is a strong trend towards the Euclidean distance reaching an asymptote after approximately 25 iterations of the gradient boosting algorithm, and therefore this will not create a meaningful barrier to analysis. At 25 iterations of gradient boosting there is reasonable improvement at the margin for increasing the number from one to two, from three to four, and from five to six but there is no detectable improvement after six centroids. Therefore, k=6 will be selected for analysis on the following basis:

- Figure 38 indicates there is unlikely to be a major improvement from increasing the number of centroids beyond k=6, and each additional centroid greatly increases computation time. Therefore k=6 is the simplest parameterisation consistent with obtaining the results needed for Section 5.6.
- k=6 is consistent with the findings of the t-SNE technique in Figure 36

- Although there is a small improvement in Euclidian distance from moving from k=6 to k=9, a sensitivity analysis of k=9 performed in Appendix D.4 suggests that k=9 may overfit the data whereas k=6 generates robust and meaningful results.

5.5.2. Centroid weighting

Table 11 gives the results of the clustering algorithm for six centroids. No post-processing was applied except rearranging the order that the Clusters were presented in Table 11 compared to the raw analysis. Certain cells are highlighted to give an idea of where the algorithm identified meaningful cleavages between the datapoints, although note that no statistical test is made for these differences.

Table 11 – Weightings of kNN clustering algorithm for six centroids

	Centroid	1	2	3	4	5	6
	Distribution	**25%**	**27%**	**14%**	**5%**	**7%**	**23%**
1.1	Binary cost-effective – Base case	1.00	1.00	1.00	0.00	0.00	0.00
1.2	Binary cost-effective – Societal Perspective	1.00	1.00	1.00	0.00	0.00	0.00
1.3	Binary cost-effective – 'Capping' technique	1.00	1.00	0.44	0.00	0.00	0.00
1.4	Binary cost-effective – 'Tapering' technique	1.00	1.00	0.00	0.00	0.02	0.00
2.1	Proportion of NHS budget spent in peak spending year	0.05	0.01	0.14	0.00	0.45	0.04
3.1	Binary variable – is the QALY gain using standard methods 'significant' (i.e., >12)?	1.00	0.00	0.00	0.17	0.00	0.00
3.2	Proportion of patients made worse off by the intervention	0.00	0.01	0.15	0.05	0.27	0.82
3.3	Total value of health lost by patients made worse off by the intervention	0.01	0.00	0.03	0.14	0.04	0.20
4.1	Index value for Rawlsian justice	0.23	0.15	0.17	0.06	0.14	0.12
4.2	Index value for Vertical justice	0.02	0.05	0.05	0.14	0.06	0.09
4.3	Index value for Horizontal justice	0.08	0.12	0.13	0.15	0.13	0.15

Value notable for being high (indicative only) Value notable for being low (indicative only)

5.5.3. Clusters identified

The purpose of conducting clustering analysis is to identify mathematical clusters of data in 16-dimensional space to allow later analysis of those clusters in the same way we can visually and easily analyse the 2-dimensional clusters in Figure 36. This is accomplished in Table 9. In order to be valuable to the research, however, it is necessary to understand what these clusters 'mean' in ordinary HTA terms.

As with all data analysis projects, it is valuable to present the data in summary form (Severance, 2016). Table 12 displays a summary table of these outputs, while Figure 39 replicates the PSA cloud from Figure 35 but overlays the clusters as identified by the kNN algorithm. Figure 40 displays a detail from Figure 39 to help make the distinction between Cluster 2/3 and 3/4 clearer (although note that the distinctions between these clusters nevertheless mostly exists in the equity and spend outcomes, and therefore is very hard to see even in Figure 40).

Detailed analysis of the Clustering Algorithm Results are given in Appendix D.5.

Table 12 – Summary data regarding kNN outcomes

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**
Percentage of all scenarios	25%	27%	14%	5%	7%	23%
Probability ICER <£30,000	1.00	1.00	1.00	0.04	0.03	0.00
Average NHS budget impact in peak year (as % of total budget)	13%	3%	12%	5%	47%	8%
Mean delta spend per patient	£73,424	£2,648	£63,806	£177,141	£225,743	£77,159
Mean delta QALY per patient	24.91	4.92	5.18	3.09	3.10	-7.35
Implied ICER	£2,947	£538	£12,310	£57,315	£72,715	-£10,499
Net Monetary Benefit (NMB)	£673,955	£145,085	£91,686	-£84,421	-£132,608	-£297,640
Probability of a meaningful (>12) QALY increase	1.00	0.00	0.07	0.06	0.02	0.00
Probability of harming a patient by enhancing them	0.01	0.03	0.13	0.11	0.15	0.83
Probability of enhancement being dominated	0.00	0.00	0.00	0.02	0.14	0.54
Probability of enhancement dominating	0.50	0.54	0.33	0.00	0.00	0.00
Probability of improving Rawlsian equity	0.98	0.83	0.91	0.77	0.89	0.39
Probability of improving horizontal equity	0.00	0.06	0.23	0.21	0.32	0.76
Probability of improving vertical equity	0.17	0.31	0.57	0.50	0.59	0.69

Figure 39 – PSA probability cloud (Figure 35) with kNN clustering applied

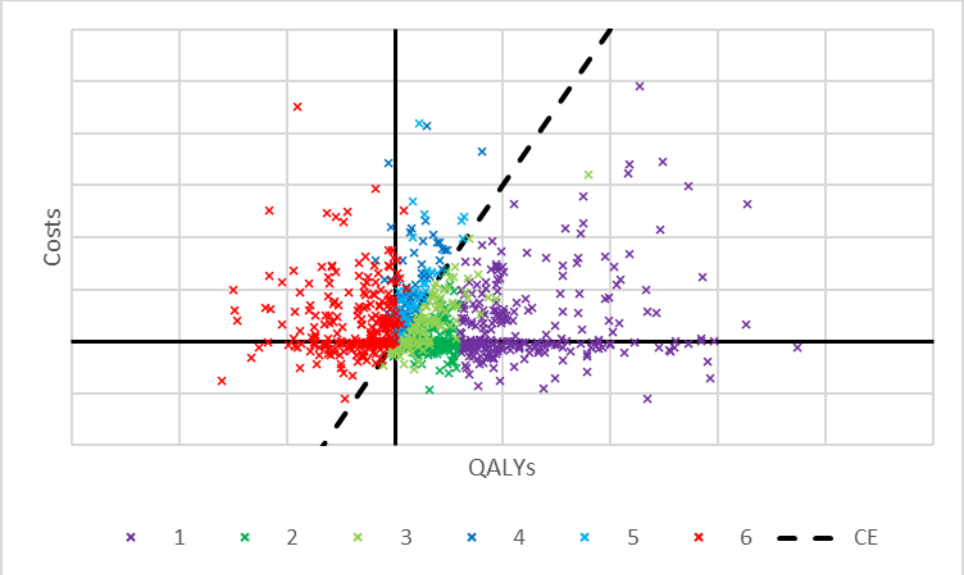
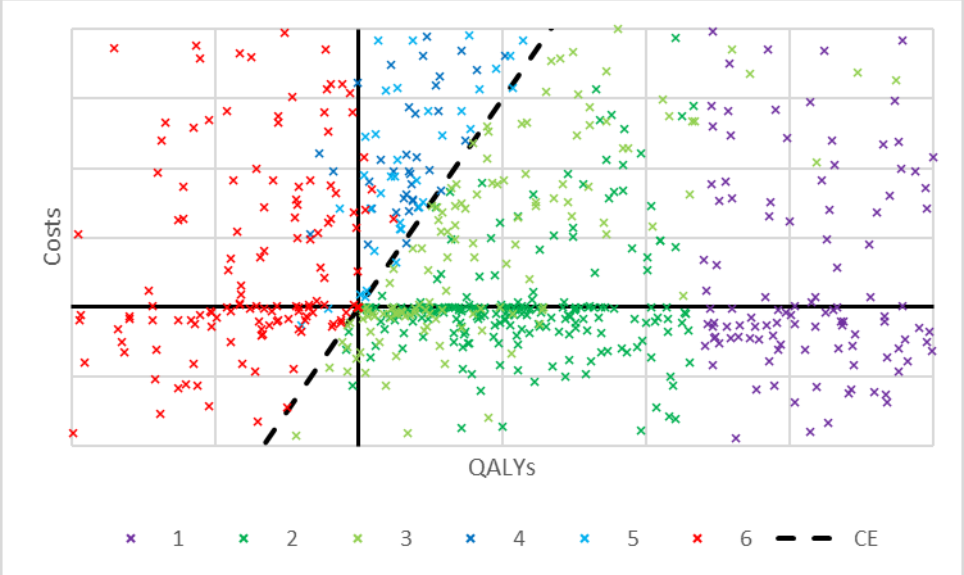


Figure 40 – Detail from Figure 39



From reviewing these data and the detailed analysis in Appendix D.5, it is possible to present a stylised picture of what cleavages the algorithm is making. Figure 41 graphically displays this result and Table 13 describes it.

Figure 41 – Stylised description of Clusters

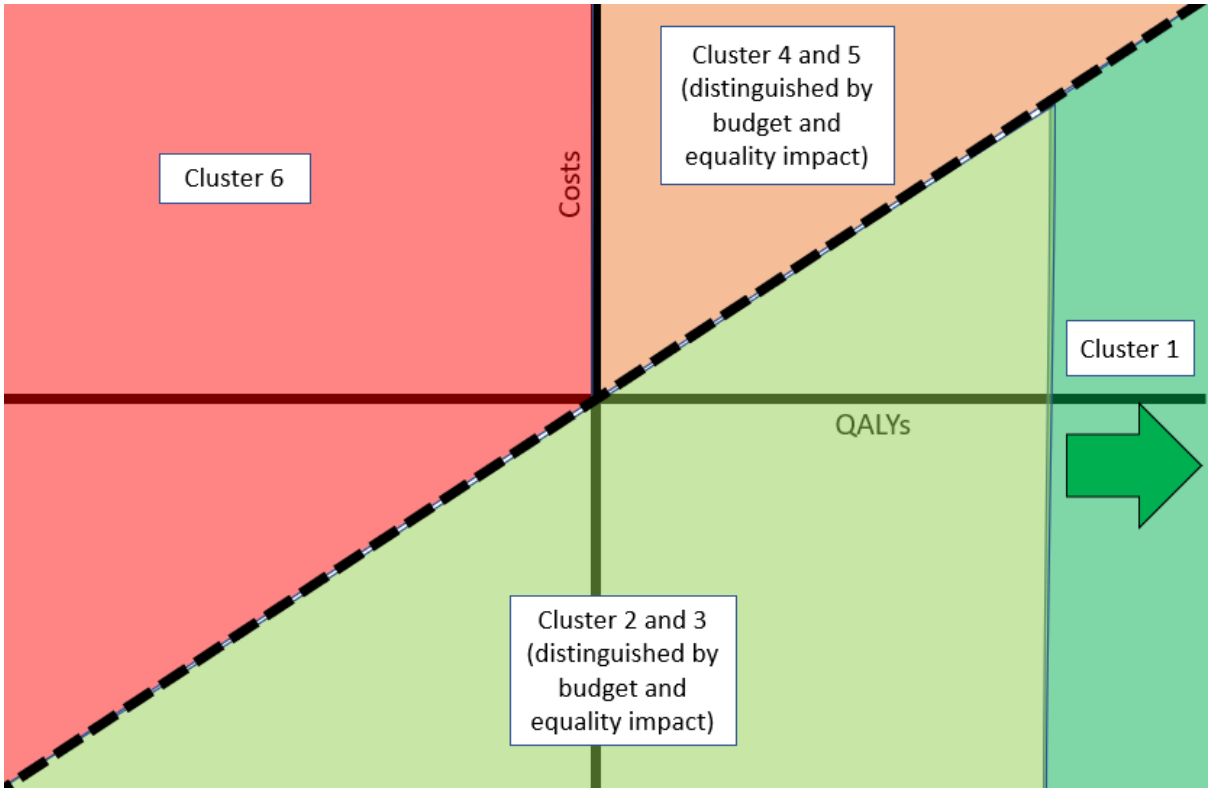


Table 13 – Generalised description of clusters

	Summary description	**Detailed description**
1	"Enhancement is a Panacea"	Always cost-effective, and always offers a large increase in QALY – the stylised social value judgement is that society desires these enhancements even if they replace conventional NHS care
2	"Enhancements are Conventionally Cost-Effective"	Always cost-effective, and usually dominant – this is equivalent to existing non-enhancement technology
3	"Enhancements are Cost-Effective only because of their QoL > 1 Effects"	Always cost-effective, typically very expensive, but key distinguishing feature is that this Cluster is NOT cost-effective if enhancement effects are ignored in analysis.
4	"Enhancements are Not Conventionally Cost-Effective"	Never cost-effective, and typically contains costs and QALYs consistent with an ordinary HTA – this is equivalent to existing non-enhancement technology
5	"Enhancements are Staggeringly Expensive"	Never cost-effective, and use up a significant proportion of NHS resources, far outside the scope of an ordinary HTA – the stylised social value judgement is that society desires these enhancements but not to the extent they displace conventional care
6	"Enhancement is Unapprovable"	Either dominated or not conventionally cost-effective in the SW quadrant – the stylised social value judgement is that society would pay to avoid these anti-enhancements

5.6. Discussion

5.6.1. Coherence of theories

The purpose of exploring the full enhancement space is to establish whether any of the 13 theories identified in Table 8 fail unexpectedly when confronted with a technology outside the author's expected parameters for an enhancement. To that end, we can straightforwardly answer the question of whether there are any internally consistent theories of health-related human enhancement by simply assessing each theory against each cluster and identifying if there are any theories which produce consistent results for every cluster. As described in Section 2.3 and Section 4.6, the concept of 'consistent' is not entirely well defined; what is meant is that the theory doesn't perform catastrophically worse on one particular enhancement-cluster. However, it is understood this approach necessarily allows a certain degree of flexibility in the analysis and therefore the discussion should be read in conjunction with the summary analysis in Table 14.

Table 14 summarises the responses, and highlights where a case could be made for inconsistency of response. Perhaps the most important finding of the entire thesis is that there is at least one consistent response to the health economic challenge of enhancements, and that therefore other theories with harder bullets to bite can be assessed against that option as the next best alternative (rather than 'the complete collapse of the NHS', which might indicate that significant levels of inequity / inefficiency could be tolerated as an alternative).

Table 14 – Contingency table for theories of human enhancement versus possible enhancement characteristics

Index	Approach	Cluster 1	Cluster 2	Cluster 3	Cluster 6
		"Enhancements are a Panacea"	**"Enhancements are Conventionally Cost-Effective"**	**"Enhancements are Cost-Effective only because of their QoL > 1 Effects"**	**"Enhancement is Unapprovable"**
1.1	Conventional HTA process (NHS / PSS perspective)			NHS Subversion	
1.2	NHS stops existing and converts to US-style HMO-led market	We might regard access to these enhancements as a human right, and this cannot be guaranteed in a free-market system	No significant risk of NHS Subversion, but potential for significant resulting inequity		
1.3	Mixed-market system			NHS Subversion	
2.1	Conventional HTA process (societal perspective)			NHS can still be Subverted, and this may be more likely given enhancements could also affect productivity domains	

2.2	Societal perspective plus government subsidy for prosocial enhancement			Does not solve problem of NHS Subversion, and additionally far more expensive making it likely less efficient overall	May make some of these enhancements desirable to prescribe despite their harming patients if they are subsidised for the NHS (similar to SW quadrant now). This is undesirable from the perspective of the individual patient, but may be desirable from the perspective of patients generally if the subsidy is large enough to cross-subsidise other spending.
2.3	Societal perspective plus government mandate for prosocial enhancement			Does not solve problem of NHS Subversion, but is at least more efficient than 2.2	May mandate the use of some non cost-effective and harmful enhancements for their prosocial benefit. This is undesirable for the recipient, and also offers no compensating value to the NHS. Society as a whole might consider the tradeoff desirable.
3.1	Economic Disincentives Model	We might regard access to these enhancements as a human right, and this cannot be guaranteed under EDM		Should offer little to no risk of NHS Subversion. However, intense inequity a likely result.	

4.1	Ban on all technology which could potentially enhance	Highly repugnant conclusion that we would fail to use technology to help those with diseases in order to protect those with diseases from unrelated downside of the same technology - generally fails ethical test of helping those who we can costlessly help if at all possible			
4.2	Ban on all technology used 'principally' to enhance	Depending on details, potentially same ethical concerns as 4.1	Potential for moral hazard at the margin		
4.3	Heavily disincentivise enhancement with ‘cap’ on QoL > 1			Potential for moral hazard at the margin	
4.4	Heavily disincentivise enhancement with a ‘taper’ on QoL > 1				
5.1	Attempt to minimise inequity				Potential risks of involving these treatments in a 'levelling down' process

5.2	Compensate those who cannot / do not wish to be enhanced	Likely leads to significant equity issue, that Cluster 1 enhancements devalue the worth of a QALY so that *ex ante* compensation is less desirable than enhancement		Does not solve problem of NHS Subversion, and additionally far more expensive making it likely less efficient overall	

Arguably, position would involve a difficult tradeoff but one which could be reasonably advocated for

Arguably, position so inconsistent / tradeoff so one-sided nobody could credibly advocate for it

NB That Cluster 4 - "Enhancements are Not Conventionally Cost-Effective" and Cluster 5 - "Enhancements are Staggeringly Expensive" excluded for reasons of space (since they present no novel issues of resource allocation in a human enhancement context)

5.6.2. Strengths and weaknesses of economic model

5.6.2.1. Philosophical assumptions of modelling

The choice of methodology is a great strength of the economic model. Although the choice of microsimulation modelling to build theory is unusual, it is well justified in Section 4.2 that this is the only reasonable approach to enhancements. Beyond this, the methods are straightforward and the opportunity to use a clustering algorithm to draw insights from a multidimensional model output is a strong argument in favour of the theoretical position taken in this thesis.

However, the model embeds assumptions which reflect the broad consensus of the academic health economic community now, but may not do so in the future. For example, the model treats the societal perspective as being an alternative to the default NHS / PSS case, but there is at least a reasonable argument that societal perspectives offer more accurate valuations of the social value function in HTA assessment(Miners, Cairns, & Wailoo, 2013). Perhaps more enhancement-specific, the model treats all externality costs and benefits as being fungible in the societal case – that is, QALYs generated outside the NHS are exactly the same as QALYs generated inside the NHS. This is a reasonable assumption now because in general the QALYs generated outside the NHS as a result of an NHS intervention are negligible (with the possible exception of fertility interventions, which have already been noted as another special case of modifying HTA rules to avoid repugnant conclusions – see Narveson (1973)). However, in a post-enhancement world this might not be true. Perhaps the majority of QALYs will be generated outside the NHS, for example because cancer-fighting nanobots in our bloodstream receive service updates from a central computer outside the NHS (Resnik & Tinkle, 2007), and therefore a more formal approach to valuing QALYs generated inside and outside the NHS will be required.

It is possible to over-think this weakness of the model – structural assumptions are varied substantially and the methodology of the model is not supposed to lead to accurate predictions of the future HTA landscape, but it is worth considering when drawing conclusions that state-of-the-art HTA techniques may change over time, and therefore the parameters for the best response to enhancements will change in lockstep.

5.6.2.2. Comprehensiveness of modelling

A second strength of the model is that it comprehensively explores the available enhancement space, taking a systematic approach to identifying descriptions of enhancement in the literature, modelling these descriptions flexibly into the model and then using an expansive clustering technique to ensure that the entire space was well searched.

This does suggest a second key weakness of the economic model though, which is that it is only able to explore enhancement-space which is in some sense touched upon by the process above. A simple demonstration of why this matters is to note that genetic enhancements are deliberately excluded from the review on the grounds that they create legal issues which health economists are unequipped to comment on. However, in real life the NHS will not be able to just ignore legal issues stemming from the modality of the enhancement, and therefore the structural assumption in the model of modality agnosticism is – fundamentally – inaccurate to real life.

Of course, it is a famous aphorism that all models are wrong (but some are useful) (Box, 1976). The concern is that the model may miss some genuinely important economic insights rather than that it fails to exhaustively describe every possible kind of enhancement. There are some signs that enhancements might potentially possess characteristics that are not shared by any existing medicines and therefore might require insights from an economic discipline outside health economics. For example, we might imagine an enhancement which created a collective consciousness as part of the enhancement process (or as an end in itself) – perhaps an enhancement which allowed high-fidelity transmission of complete concepts to someone with compatible detection equipment as an adjunct to the ordinary process of describing an idea. The more people who join this collective consciousness, the more value there is in others joining, a principle in economics described as a 'network effect' (Anomaly & Jones, 2020). If enhancements can offer an externality benefit on enhancement itself – see for example Katz and Shapiro (1994)) – then the paradigm of most HTA agencies will make serious errors.

Figure 42 – Model output for network effect case where 5% of people are networked

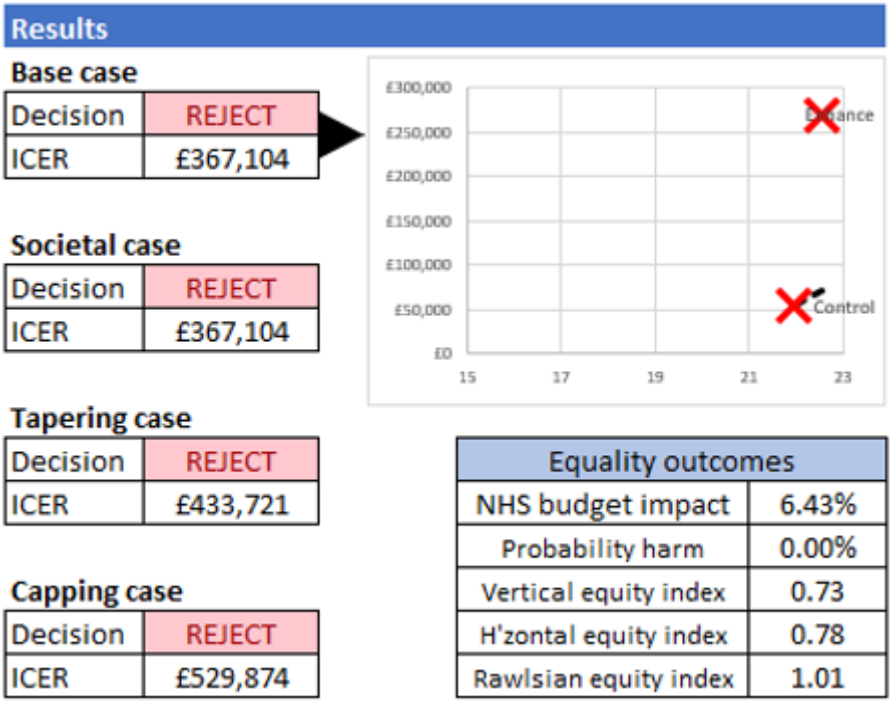
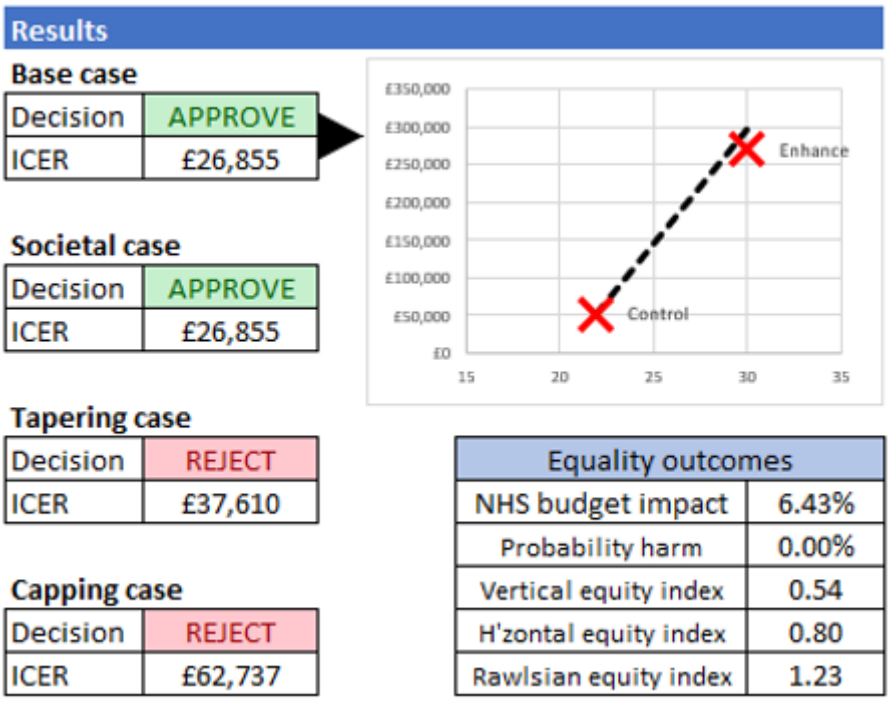


Figure 43 – Model output for network effect case where 95% of people are networked



The problem is not that the model *cannot* consider network effects. Figure 42 and Figure 43 show that, unsurprisingly, the scenario above results in an 'approve' decision for any realistic value of the network effect, but a strong 'reject' decision at the margin, necessitating a change of methods regardless of the more general approach adopted by HTA agencies. The problem is more that this is a

genuinely important insight which would have been missed save for knowing of the relevant paper through background reading rather than the systematic review. To a certain extent this problem could be ameliorated through a more encompassing review (Anomaly and Jones (2020) was rejected as it was about genetic enhancement), but even this approach cannot identify papers which have not yet been written about ideas that don't currently exist.

Sensitivity analysis around the network effect is given in Appendix C.3 which confirms that enhancements which create network effects create significant problems for existing HTA methods separate from the NHS Subversion effect.

5.7. Conclusions

As discussed in Chapter 4, it is not possible to identify 'the best' approach to the HTA of enhancement technologies. Different approaches will have a different profile of tradeoffs, risks and outcomes and selecting one approach from this frontier is a difficult decision which would presumably be taken in consultation with NICE and NHS stakeholders.

The method adopted to search the enhancement space is a clustering analysis of a probabilistic sensitivity analysis using kNN. This is a standard tool for reducing an excessively large search space to something human tractable (Treshansky & McGraw, 2001), although the discussion of kNN vs DBSCAN is novel in the health economics literature, and the specific application of a clustering algorithm to a probabilistic sensitivity analysis is novel in the literature as far as I am aware (although the more general case of machine learning on an artificial dataset is not – see for example Kwakkel and Pruyt (2013)). While the nature of clustering algorithms is such that different parameterisations will produce slightly different results, in general this approach gives good certainty that there are around six major health economic clusters of possible enhancement techniques that could be invented in the future.

The six clusters presented in Table 13 represent conceptually different routes enhancement technologies might take. This is an important finding, since it greatly refines a somewhat strange tendency in the literature where the modality of enhancement is excessively discussed but the actual policy relevant features of enhancement technologies are assumed to be homogenous. As a result of

this analysis, we can explain why some authors appear to take diametrically opposed views to others on the correct response to enhancement; someone who imagines that enhancements will mostly be of the panacea-like Cluster 1 (perhaps Savulescu et al. (2011)) would regard equity concerns as being secondary to the enormous societal benefits enhancements could bring. Someone who imagines enhancements will mostly be in the enormously expensive Cluster 5 (perhaps Sparrow (2015)) probably would imagine that equity concerns trump the very minor efficiency gain from allowing a private market in these enhancements. Even the NHS Subversion effect, which has been underpinning and motivating most of this thesis, is only really a problem if Cluster 3-type enhancements are created – existing HTA processes mostly cope well with enhancements in any other Cluster. It is perhaps a little surprising that authors (including myself) have not intuitively seen that the features of the enhancements themselves make a big difference to the NHS' optimal response to them, but now that this has been demonstrated it is clear that future policy recommendations on enhancement should be extremely specific about what features of the enhancements must be the case before the policy applies.

Table 14 summarises the main output of this thesis. It compares each HTA approach to enhancement identified in Chapter 4 with each enhancement type-cluster identified in Chapter 5. Broadly speaking, it appears that at the very least there are a number of possible approaches to enhancement which will allow the NHS to continue to operate in a manner no worse than existing practice, and at least one position (4.4 – 'Tapering' QALYs) which has no major tradeoffs compared to existing practice. Various authors – such as Savulescu (2005) – might argue that enhancements offer the opportunity to do better than merely 'no worse than existing practice' and that therefore the choice of HTA policy approach is not obvious despite the 'Tapering' proposal appearing strong in Table 14.

Another interesting trend the table highlights is that enhancements of Cluster 5 – stylised as having positive health benefit but too expensive for any individual or government to realistically consider – are not really affected by any HTA approach; no matter the approach, these enhancements are undesirable under any social value function. This is interesting, because to a large extent this is the position that enhancements are currently in – there is a large body of evidence about (for example)

chemicals which can increase intelligence (Brühl, D'angelo, & Sahakian, 2019) but the process of making these chemicals available on the NHS (i.e. the process of conducting Phase 3 trials and the risk of a rejection at HTA assessment) apparently means that the chemicals cannot be sold at a price that makes this commercially attractive. One of the key arguments of this research is that policy-makers have not really understood the potential seriousness of enhancements on the NHS, and perhaps one reason for this is that any survey of existing health-related enhancements would indicate that no matter what approach is taken the conventional HTA approach is just as good. However, this is not true of enhancements of any other Cluster and therefore hides the potential seriousness of the problem if enhancements are invented or refined that behave differently.

Overall, it seems likely that the question posed in Chapter 1 – can we identify a set of internally consistent HTA approaches to human enhancement? - has a definitive answer, which is that we can identify such approaches; the methodologies described in this thesis can be replicated if there are advances in bioethical thinking, and based on the state of the art at the time the thesis was written bioethicists have identified several routes the NHS could choose to explore as part of their response. Further health economic work in the area should build beyond merely highlighting possible approaches, and focus on which of the tradeoffs identified in Table 14 could potentially be acceptable to the public, and which are too radical to adopt even to prevent Subversion.

Chapter 6. Conclusions

6.1. Introduction

Whether bioconservatives or bioliberal, ethicists are almost unanimously in agreement that enhancements "change the rules of the game" (Coeckelbergh, 2013) and could radically reshape and restructure society. The concept of NHS Subversion (Section 2.2) was an illustration of how enhancements could change the rules of the 'health technology assessment'-game, a subject of keen interest to me as a health economist. However, throughout the thesis it has become apparent that enhancements require a very flexible way of thinking wherever they occur. In Chapter 2 we find that defining an enhancement is a significant challenge, in Chapter 3 new methods of systematic review are employed to try and capture insight on enhancements that would otherwise be missed, in Chapter 4 novel approaches such as microsimulation and Multiple Criteria Decision Analysis are used to try to capture the range of domains over which enhancements might operate and finally in Chapter 5 exploratory machine learning is used to try to reduce the total enhancement-space to something human tractable.

The result of this unorthodox and challenging approach is perhaps not as exciting as the journey to get there; yes, enhancements may present a problem for HTA agencies if and when they are invented, but there are a range of approaches which those agencies could adopt to prevent catastrophic collapse of their respective NHSes, and at least one (a 'Tapering QALY' approach) which appears to offer no worse outcomes than existing HTA methods but which is resistant to the Subversion effect.

6.2. Policy implications

6.2.1. Identifying the best approach

Although this thesis contains a clear policy implication that existing HTA methods are inadequate for the assessment of enhancements, it does not make a recommendation on which HTA method should replace it. This is because the problems are underspecified, for at least three reasons.

1. The first is that it may be possible to specify more fully what enhancements the NHS can expect to have to review, and therefore add a few approaches to the list of possibilities – that is, remove the restriction that we are 'agnostic' about which Cluster(s) enhancements will

belong to. In Section 4.6.4.3 it is noted that Ray (2016)'s proposal would also resolve the issue of NHS Subversion as long as we could be confident that a wide range of Cluster 3 enhancements were invented which improve outcomes across many different health domains.

2. The second is that these approaches come with tradeoffs – especially the EDM which would require a very fundamental restructuring of the NHS now in order to prepare for enhancements later. If these tradeoffs are unacceptable, then it may be that the rational approach is to take no action and hope that no Cluster 3 enhancements are invented (or accept an *ad hoc* system of enhancement HTA is the only possible outcome).
3. The third reason the NHS should not immediately switch to one of these three proposals is that society may find that enhancements fundamentally redraw the role of the NHS. For example, the HTA approach proposed by Lavazza (2019) would actually exacerbate the problem of NHS Subversion by adding additional cost to each enhancement undertaken, and so despite its many interesting features would do no better than existing HTA methods at preventing the NHS' collapse in this situation. However, this is not to say Lavazza (2019)'s proposal is incorrect (or even strictly inferior to using existing HTA methods) – it could well be that Lavazza (2019) has seen further than the relatively circumscribed argument of this research and identified that in a world with capacity-altering enhancements equity for those who cannot participate in the enhancement 'rat race' (Sparrow, 2015) becomes more important than free access to therapeutic healthcare at the point of need.

Furthermore, this thesis actually understates the problem slightly, since Section 5.6.2 identifies that there are some enhancements with features that could be problematic regardless of the HTA approach adopted, and the entire NHS / government decision-making apparatus would fail to respond adequately to them. For example, in Chapter 2 enhancements where the benefit of enhancement is endogenous to the number of individuals who receive that enhancement were discussed, and the only plausible solutions to these is intense government regulation of those specific enhancements (other examples are given by Rajczi (2008)). Notwithstanding the problems of the health economic response to enhancement, policymakers will also have to balance competing concerns across multiple other

domains, including clinical (Asscher, Bolt, & Schermer, 2012), legal (McGee, 2020), and perhaps even theological (Tomkins, 2014).

6.2.2. Reasons for altering our base case HTA assumptions

Although this thesis does not recommend specific policy proposals, there is a strong case made that all future HTA policy proposals for enhancements should be compared against the 'Taper QALY' approach rather than the default HTA approach in future. The 'taper' approach is particularly interesting because it does not imply a radical redesign of NHS services – simply an alteration to existing NICE methods to account for the possibility of an enhancement causing budgetary issues for the NHS. The downside of the approach is that it creates discontinuities in the otherwise smooth ICER calculations, and this can lead to perverse behaviour – for example deliberately injuring oneself to gain access to particular enhancements ('moral hazard'). Nevertheless, the ability to restructure a potentially existential problem for the NHS if faced with any 'Cluster 3' enhancement into a problem of moral hazard when faced with very specific enhancements on the borderline of Clusters 2 and 3 seems like a significant improvement, and the fact that it can be done without altering anything other than the HTA methods means that the solution is significantly more tractable than the radical redesigns of the entire NHS required by a number of other proposals.

However, this approach needs significant further conceptual work to be fit for purpose. The manner and method of tapering would need to be considered. Some encouraging signs that this might be possible are to be found in comparing the most recent NICE Methods to the Methods which were available during the bulk of drafting this thesis. Using NICE as a proxy for all HTA agencies, we see a recognition that certain QALYs actually might be worth different amounts from other QALYs, and specifically QALYs which address radical absolute or relative QALY shortfall are valued up to 1.7x higher than QALYs which do not. Inverting this approach could lead to conclusions of the sort that QALYs which address a 'nice to have' better-than-perfect health need are valued up to 1.7x less than QALYs which do not, although it should be noted that simply inverting the approach of the new NICE methods is nowhere near radical enough to prevent NHS Subversion – the value of a QALY must eventually either be or asymptote towards zero for the 'Taper QALY' approach to work.

I conclude that this is an issue of empirical ethics from this point; society must specify a schedule of tradeoffs it is willing to make regarding conventional health versus enhanced QALYs, and then some tapering method which fits society's preferences found to apply to future HTA decisions. Rather neatly, the QALY framework sidesteps one of the most difficult conceptual issues in the thesis (distinguishing therapy from enhancement) when adopting this approach.

6.3. Conclusions

Overall, this thesis attempts to bridge the gap between the two separate and (sometimes, it appears) foreign disciplines of health economics and bioethics, to produce what I believe is a novel and important result regarding the impact of 'better than perfect' health human enhancement technologies on publicly funded healthcare systems ('NHSes'). Part of the challenge of this approach was a need to be highly flexible with respect to methods, especially around the Systematic Literature Review and economic modelling approaches.

As a result, there are weaknesses in the thesis that limit how strongly any conclusions can be made. The most significant is that enhancements are (mostly) hypothetical technologies at the moment. The only limit to hypothetical technologies is our imagination, and therefore this thesis has only been able to explore enhancement-space where there is existing conceptual bioethics literature to provide structural variation in the resulting probabilistic sensitivity analysis. The results and discussion could be entirely overturned by a single strong counterexample of an enhancement which does not share the properties it is theorised that enhancements will all share in the economic model, and - in some sense - there is no way of knowing how severe a limitation this is until it occurs and the results are tested.

A similar limitation exists in the conceptual framework used to consider the impact of enhancements – while a health economic perspective is certainly an important one, alternative approaches bringing in different disciplines like law and medicine might result in entirely different classification schema, or even different conclusions entirely. This limitation is apparent throughout the work – for example a decision was made to exclude genetic enhancements from the literature review because of my lack of interdisciplinary knowledge about the legal and medical implications of such enhancements, despite it being a key topic of interest to bioethics authors.

By design, this thesis only makes preliminary inroads into the question of what approach should be adopted by HTA agencies. While proving that there could exist approaches other than letting the NHS become Subverted is an important conceptual step, future researchers wishing to build on this thesis will have a significant number of questions to answer. In particular, I conclude the four key next steps for future research are:

1. To establish the exact schedule of tradeoffs society will tolerate for the 'Tapering QALY' approach, to use as a benchmark for future theories of HTA assessment of enhancements
2. To establish the risk of moral hazard in adopting the 'Tapering QALY' approach, and consider methods to minimize this risk.
3. To establish whether any alternative theory of HTA assessment of enhancements offers sufficient benefits against the 'Tapering QALY' approach to compensate for its disadvantages
4. To investigate novel proto-enhancements to ensure they are of Cluster 5 (or perhaps Cluster 2 at the absolute margin). Any other type of enhancement could have the potential to Subvert, and therefore a program of work setting up a horizon scanning 'enhancement observatory' could be important in giving the NHS warning of risky pipeline technologies.

Furthermore, the experience of working in a cross-disciplinary way in this thesis has led me to reach some more general conclusions about interactions between bioethicists and economists in the future. Specifically, health economists could make bioethicists' work easier by helping them 'translate' their ideas in a way that preserves economic insight (for example by providing simple economic models which bioethicists can tinker with to ensure that their ideas 'translate' properly), while bioethicists could more explicitly consider costs and tradeoffs when making policy proposals. Dubljević (2013a)'s Economic Disincentives Model is an example of how this might work in practice, although even Dubljević sometimes struggles with the mathematical rigour needed to properly communicate an economic concept.

The key motivation for pursuing this thesis was a belief that enhancements were a potentially important but understudied topic in health economics. The results presented above bear this

conclusion out; enhancements do have the potentially to radically upend existing health systems. HTA approaches which are designed for humans of an ordinary lifespan living more-or-less ordinary lives may not scale into a world where enhancements can routinely add 80 QALYs to a single individual, as occurs in Section 5.2. At some point enhancement QALYs may become so abundant that they represent a genuinely existential threat to a model of publicly funded healthcare. More generally, the potential impact of 'better than perfect health' on the HTA system and NHS more broadly is significantly underrated by policymakers, which might explain why the topic is understudied in the literature. This is potentially because they are receiving inadequately 'translated' advice from bioethicists, who do not know what the health-economically relevant characteristics of enhancement technologies are likely to be.

Like Bostrom and Savulescu (2009b), I believe the next few years offers the final opportunity to productively debate the challenge of enhancement and HTA before the issue is completely swallowed by the broader bioliberal vs bioconservatives debate. I am extremely pleased that this thesis is able to make a number of meaningful – if modest – contributions to that debate.

Appendix A. Additional material on Chapter 2

A.1. Detail on three concepts of health

In Section 2.3.3.2, the literature on health is summarised as being broadly comprised of three categories in Table 1. These are the biological, functional and social models of health. Details on these three models are unnecessary for the broader point of Chapter 2 (that no definition captures exactly what health is) but a complete account is required to ensure that no 'cherry picking' of definitions has occurred. Therefore, a fuller description of each concept is presented below.

A.1.1. Biological model

The first account of health is one which sees the human body as comprised of biological systems which can malfunction in a variety of ways – bacterial infection, cancerous malignancy, physical insult and so on (Boorse, 1975). Someone might be said to be healthy if they have an absence of malfunctions in their biological systems, and therefore the goal of healthcare is to correct the cause of the malfunction. This model of health is how the medical establishment has treated medicine until at least the early twenty-first century (H. Wilson, 2000). It is sometimes described as an 'objectivist' position in the literature (Pisanelli, 2004; Sarkar & Plutynski, 2010).

This account has significant intuitive appeal and explanatory power. For the vast majority of illnesses, a specific biological cause such as a pathogen can be identified under a microscope or on an x-ray, and the removal of the cause of disease usually restores health in short order. Mental health conditions are slightly less amenable to this explanation, but since treatments for mental health conditions often involve modification of brain chemistry it seems only a short and reasonable step to say that if the mental health condition responds to a change in brain chemistry, then the brain chemistry was probably responsible for the condition.

It may initially appear like the biologic account could have nothing to say about human enhancement; since enhancement involves making a biological system function better than normal then by definition

the biological account can support a therapy / enhancement distinction (with the cleavage being whatever definition is used to generate a concept of 'normal'). However, any reasonably sophisticated biological model will account for this. For example, Boers and Jentoft (2015) describes disease as an accumulation of impairments that build up in an individual and create a predisposition to certain negative outcomes (for example, death). This neatly explains diseases that have multiple biological causes; for example, this framework has been used to characterise frailty as a disease (Rockwood & Mitnitski, 2007). For our purposes, it allows for the possibility that enhancements can reduce the predisposition to negative outcomes beneath the level of a baseline human.

A.1.2. Functional model

The second account of health is one that sees health as being constituted by a variety of functions necessary to cope with the demands of daily life. For example, Ménière's disease is a disorder of the inner ear that leads to progressive deafness (Sajjadi & Paparella, 2008). The deafness can be treated with a cochlear implant, a medical device that simulates the way that the ear receives and produces sound (in fact it appears that the cochlear implant may treat all symptoms of Ménière's disease (Desiato, Patel, Nguyen, Meyer, & Lambert, 2020), but we focus here on the deafness aspect only). By the biological account of health an individual with Ménière's disease is not healthy; although the cause of the disease is unknown, it is clearly the result of some problem with the ordinary machinery of hearing in the human body and therefore represents a biological failure of some kind. Yet there is a case to be made that 'hearing' is not actually meaningfully important for coping with the demands of daily life; in fact, in order to navigate the world successfully it is merely important that you are able to 'use language' (Kermit, 2012) – whether that is spoken language as for most people, sign language for people with Ménière's disease or some third option that nevertheless allows the function of 'using language' to be fulfilled (e.g. writing, text-to-speech, mime etc). There may – in reality - be a meaningful difference between being able to hear and not being able to hear, but if that is the case it is potentially only because society puts barriers in the way of non-hearing ways of engaging in a community of language-using individuals (by analogy, consider that we would not regard someone as 'unhealthy' if they went on holiday to France without being able to speak French, even though French society has placed barriers in the way of their ability to function there).

This account too has some intuitive appeal; it identifies that people realistically do not have access to information about their organ's biological effectiveness, but can make judgements about their activities of daily living. Counterintuitively it does suggest that a person could be 'healthy' while also suffering from one or more disease as defined by the biological model (provided those diseases did not interfere with the person's functional abilities) but this is actually reasonable consistent with how the term 'healthy' is used in ordinary language (R. Smith, 2008) – a simple example would be a short-sighted individual who wears spectacles. Note that there may be some considerable overlap between the biological and functional model, since both rely on 'functions' in their definitions, although the biological model talks about the function of particular organs whereas the functional model talks about the functions of individuals in a society.

This account suffers a little from an inability to specify exactly what a 'function' is. An early and popular definition is given in Wright (1973):

- "A **function** of X is Z means: (a) X is there because it does Z (b) Z is a consequence (or result) of X's being there"

This definition is not quite adequate, since it "tends to see functions where there are none" (Cooper, 2002) – for example consider a fat man who does not exercise because he is so fat that it embarrasses him to go to the gym. According to the Wright account, the fat tissue has the 'function' of preventing exercise; being fat is the cause of the man not exercising, and he is fat because he does not exercise (Boorse, 1975). It also fails to account for reasonable edge cases which crop up in everyday life; there are plenty of failures to function which are not diseases, such as wearing ear plugs at a rock concert to prevent hearing certain frequencies, or taking the contraceptive pill to prevent pregnancy. Flew (1973) concludes that if a person could decide to function normally then a failure to function is not a disease. Similarly, Cooper (2002) suggests that some conditions are so well managed that they are not failures to function despite clearly being diseases; for example, an asthmatic might never have an attack of asthma in their life thanks to regular use of their inhaler, but we would still regard them as having the disease of asthma.

However, as with the biological model, more sophisticated accounts of functioning allow for a definition of function which mostly accords with common sense. Table 15 below lists a few important definitions of functioning found in the literature. Unlike the biological model it is straightforward to see how the functional account could fit with a theory of enhancement; for example if Sen's Capabilities Approach was chosen as the particular model employed (Sen, 1974), an enhancement would be an intervention which improves the 'conversion factor' of capabilities into functionings beyond human baseline (for some given list of important capabilities, such as that proposed by Nussbaum (2003)). For example, maybe an individual who was unable to both work full time and care for a child might be enhanced to not require sleep, granting the capability to do both rather than having to pick which function was converted into a capability (Basu, 1987) - although note that Sen's approach is not specifically restricted to health, and he would argue that capabilities include many things the NHS would not normally consider health-related, such as the ability to buy and sell on the free market (Sen, 1999).

Table 15 – Non-exhaustive list of specific models of the functional account of health

Approach	**Functional account**	**Key reference**
Adaptive fitness	Ability to successfully propagate genetic material to the next generation – not seriously proposed, but often a useful toy model since we might expect health and adaptive fitness to track closely	Méthot (2011)
Statistical normalcy	Ability to do the sorts of things a typical member of your species can typically do	Boorse (1975)
Adaption	Ability to adapt to environment / adapt environment according to personal circumstances	Books (2009)
Vital goals	Ability to pursue goals which will leave an agent minimally satisfied in the long run	Nordenfelt (1995)
Modified vital goals	Amendment to the above – goals are specified as the goals that would be chosen by an idealised version of the self, to avoid people with low ambition settling for lesser states of health	Richman (2004)
Capacities approach	Stresses importance of 'capacities' – the substantive opportunity to achieve functional ends	Sen (1974)

A.1.3. Social model

The biological and functional models of health broadly fit into an objectivist paradigm (Pisanelli, 2004; Sarkar & Plutynski, 2010), meaning they tend to regard the disease and ill health as "grounded in [the?] desirability (or goodness) of an objective goal" (Sade, 1995). One might, however, reject this assumption and see health as being entirely or mostly socially constructed – bodily processes might be regarded as a special kind of system embedded in a much wider system of social construction (Brown, 1990; Kennedy, 1981).

Some constructivist accounts reject the idea of a linkage between biology and disease except incidentally. In its most extreme form, one could argue that illness is just a kind of deviant behaviour tolerated by society in a way other kinds of deviant behaviour are not (Parsons, 1951). More sophisticated accounts along these lines include Carel (2007), who argues that health is a phenomenological state of being at home in one's lived body. As interesting as these ideas are to contemplate, NICE methods require at least some engagement with the biologic model of good health, since its HRQoL instruments including the EQ-5D are predicated on the notion of biological health (NICE, 2013). However, it is possible to construct sophisticated constructivist accounts which preserve the biological root of disease while rejecting the notion that biology is important to the definition of disease. For example, Glackin (2019) draws a distinction between the physical basis of a person's condition and questions about what makes certain physical configurations diseases and others non-diseases.

While this may seem like a strange way to define health given the wealth of evidence of specific and objective causes of most diseases, in fact it may be closest to the way society actually treats disease and disorder. For example, Harris (2010) suggests that one definition of disease could be the "ER test" (presumably, 'A&E test' in the UK); in the 'A&E test' a disease is defined as anything a doctor would be negligent if they did not attempt to treat if a sufferer turned up at A&E – this suggests a model of disease where disease is simply whatever doctors feel able and empowered to treat. This also allows the account to extend easily into concepts of enhancement, where enhancements which are

socially constructed as health are simply the same thing as health, with no complicated intermediating 'propensity to negative outcomes' or 'conversion factors'.

Furthermore, the social account of health is the only account which can intuitively handle 'social diseases' which have a negative impact on society but not the individual (Spitzer, 1999). For example, we might regard a paedophile as suffering from pathologized sexuality because their condition causes them to be attracted to young children which disgusts us, but from the point of view of the paedophile they are neither biologically nor functionally constrained in their sexuality, except insofar as society constrains them by arresting them (Spitzer, 1999). The social model of ill health does not limit descriptions of health as occurring only at an individual level, and therefore can coherently assign a pathology to paedophiles or other social diseases, such as sociopathy or being an asymptomatic spreader of an infectious disease (Cooper, 2002).

A.2. Detail on inadequacies of existing conceptions of health

In Section 2.3.3.2 it is argued that no existing theory of health is adequate for the purpose of defining a clear therapy / enhancement distinction. While a few arguments are given in the Section itself, readers may be interested in identifying further issues with the definitions. Four additional arguments are given below.

A.2.1. Diseases which are normal

Diseases which are so normal as to be unremarkable present problems for the biological and social account of disease – some conceptions of the functional account can escape the problem by appealing to the impact of a disease on a functional outcome (but some can't). Certainly, there is an issue with diseases so common that more people have them than don't (Cooper (2002) argues dental caries are good candidates for this sort of disease) – if it is more common for humans to have tooth decay than not then caries cannot be considered an abnormal state. However, there is also a problem with diseases which are rare but typical functioning for a human.

The most obvious problem with the biological account is that biological systems don't need to be 'malfunctioning' in order to create outcomes we would regard as being disease (Reznek, 1987). The menopause in women is natural behaviour of the female body functioning normally, but can cause

effects women would rather not have happen to them such as hot flushes and difficulty sleeping (see, for example, Studd, Watson, and Henderson (1990)). Medical events don't even need to be unwanted; for example, pregnancy and childbirth are important medical events – often deliberately chosen – which are not malfunctions in the slightest.

This is a particularly challenging criticism in the context of this research project, since health technology appraisal is typically industry-initiated (that is, a pharmaceutical company or medical device manufacturer asks a regulator body to determine whether their product offers value for money). This gives manufacturers an opportunity to 'condition brand' prior to their regulatory submission (D. Hall & Jones, 2008), where a case is made that a previously established non-disease is actually a disease which society would value treating – in this case it is not that a disease is so normal as to be unremarkable, but rather than an unremarkable state becomes a disease through the process of condition branding. Meixel et al. (2015) argue that this technique can occur in three ways; elevating the importance of a trivial disease to a serious one (for example rebranding heartburn as gastro-oesophageal reflux disease), redefining an existing condition to reduce the stigma associated with it (for example rebranding impotence as erectile dysfunction) and finally creating an entirely new condition. An example of disease branding is the development of 'social anxiety disorder' in the medical literature (Cooper, 2002), following the discovery of paroxetine (a drug which treats social anxiety disorder, sold under the brand name of Paxil®). The discovery of new diseases is an important function of academic medicine and doubtlessly many sufferers of social anxiety disorder greatly benefit from the pharmacological mechanism of paroxetine, but in the context of enhancement HTAs there is a risk of circular reasoning if 'condition branding' could reasonably be expected to take place; we cannot decide what things are health-related enhancement if the concept of health is malleable to organisations with a financial interest in selling those enhancements.

A.2.2. Diseases which are good to have

The idea of a disease which is good to have presents considerable problems for the biological and functional accounts, since both of these rely on appealing to some inherent 'badness' of outcome in order to delineate disease from non-disease.

In a case of ‘heterozygotic advantage’ an organism which inherits a dominant and a recessive form of a gene is advantaged over an organism which inherits two dominant or two recessive copies of that gene (usually, the two dominant genes lead to ‘normal’ health whereas the two recessive genes lead to very severe health issues (Rimoin, Connor, Pyeritz, & Korf, 2007)). The textbook example of this is the case of sickle cell anaemia; a single mutation alters a nucleotide which causes blood cells to lose their ability to carry oxygen as effectively (Serjeant, 2010). If a patient has two copies of this mutation (ie from their mother and father) then it is likely they will suffer a series of escalating health crises followed by a death in their early 50’s (Serjeant, 2010). However, sickle cell disease confers partial immunity to malaria by starving the plasmodium of oxygen as it circulates in the blood; in areas endemic with malaria sickle cell disease could potentially increase life expectancy. Therefore, it appears that under certain circumstances we would regard a patient with sickle cell anaemia as being healthier than someone without on the functional account, which seems counterinitiative to the point that we should consider rejecting the whole account. (A possible response is that once we eradicate malaria, which we should do on any account of disease, we see that sickle cell disease is only functional in the sense that it grants a capability to survive malaria, and otherwise non-functional. So, the worst you could say about this account is that it temporarily mislabels a disease in some contexts. This is still a problem, but perhaps not quite as large a problem as it might initially appear.)

Extending the idea that mutations can be advantageous in some contexts and deleterious in others emphasises the problem ambiguous mutations can cause the functional model. For example, both torsion dystonia (Eldridge, Harlan, Cooper, & Riklan, 1970) and Gaucher’s disease (Cochran, Hardy, & Harpending, 2006) may be associated with higher IQ on average. While both diseases are severely physically debilitating, they are no longer fatal thanks to medical advances, and higher IQ confers significant benefits on a person (Hartog & Oosterbeek, 1998); it is not impossible to imagine that as society places a greater premium on intelligence compared to physicality that these conditions might become ‘adaptive’ (especially if the painful side-effects could be managed to allow the patient to enjoy a flourishing life with their increased intelligence). The converse of this could also be true; perhaps anxiety disorders were adaptive when humans lived in more dangerous environments (Nesse,

1994) and therefore the body is functioning correctly for a hunter-gatherer society but incorrectly for a modern industrial society. Mealey (1995) raises the interesting point that many maladaptive personality traits are potentially of this kind, drawing attention to the classic problem in game theory of 'hawks and doves', where – for example – genes that increase the predisposition for men to be violent and promiscuous may increase their environmental fitness in a harsh world where most other men are violent and promiscuous, but decrease their environmental fitness in a nicer world where most other men will cooperate to drive out violent and promiscuous lawbreakers.

Broadly, it is almost impossible to think of a variation in human functioning which could not be functional in *some* circumstance, and therefore accounts which rely on a function being valuable appear to be either very imprecise, or effectively degenerate into a social account where socially determined conceptions of normality / function are the only criteria against which a function can be judged.

A.2.3. Diseases which share a vague boundary with a non-disease

A key epistemological critique of all three accounts of disease is that it may not be possible to find a philosophically valuable distinction between 'disease' and 'non-disease' in all cases (Reznek, 1987) – however this is especially a problem for the social account, where the problem cannot be overcome by simply declaring an arbitrary boundary between the two states.

For example, soldiers who have experienced combat often experience psychological symptoms afterwards including nightmares, isolation and survivors' guilt (J. Wilson & Keane, 2004). These symptoms are experienced on a spectrum, with the vast majority of veterans experiencing only slight symptoms occasionally and a small number unfortunately experiencing debilitating symptoms almost constantly. Of this latter group we say that they are experiencing the disease of 'Post-Traumatic Stress Disorder', but there is no single objective fact we can point to that will distinguish the least unwell PTSD patient from the most unwell non-PTSD veteran – by the nature of existing on a spectrum the dividing line will necessarily be vague (Zachar & McNally, 2017). This is not true for all diseases, and sophisticated ANCOVA statistical techniques can often distinguish disease from non-disease in cases where the dividing line is real but hard to find (Beauchaine, 2007). However, this does not solve

the problem – not only is the boundary between diseases-which-are-vague and diseases-which-are-not-vague itself vague, but there is difficulty knowing what to do when the statistical methods produce results which contradict clinical expert opinion – for example a recent paper in the area found autism to be taxonic (ie 'not vague' – Haslam, McGrath, Viechtbauer, and Kuppens (2020)), when clinical consensus is that autism is a textbook example of a spectrum (i.e. 'vague' by nature) disorder (Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018).

However, the most sophisticated statistics imaginable could not respond to a different Sorites-type objection that certain diseases result in the body becoming permanently stuck in a stable but suboptimal configuration (Cooper, 2002). For example, Cushing Syndrome causes a pathological level of glucocorticoids to be produced, which results in an unsightly build up of fat between the shoulders and – if untreated – high blood pressure and diabetes (Steffensen, Bak, Rubeck, & Jørgensen, 2010). However, far more common than Cushing's disease is a slight overproduction of glucocorticoids which is not detectable except by sophisticated laboratory tests (Steffensen et al., 2010). Therefore, the dividing line between 'the correct level of glucocorticoid production' and 'Cushing Syndrome' is genuinely vague, since some level of glucocorticoid production is necessary to the processes of life. This is probably not a significant problem for doctors, who can adjust the intensity of treatment based on the level of glucocorticoids production, but does pose a problem for accounts of disease that claim to be able to distinguish all things that are disease from all things that are not (or, more specifically, all things which are enhancements)

A.2.4. Pessimistic meta-induction as a criticism of the social account of health

Pessimistic meta-induction refers to an idea in philosophy of science that the history of science shows that many ideas which were once thought to be beyond doubt have been overturned by new evidence, therefore we ought to be sceptical of our current theories which also appear to have been proven beyond doubt (Laudan, 1981). In the context of defining health and disease, we find many examples of ordinary behaviour being pathologized and diseases being regarded as ordinary variation in the human condition. For example, the British army refused to recognise 'shell shock' (now usually called post-traumatic stress disorder) as a legitimate psychological disease until 1916 (Babington,

1990), executing at least 306 men for cowardice who they later concluded had actually been displaying symptoms of shell shock (Miley & Read, 2020). A key area of debate here would be discussions regarding whether what are currently termed ‘disabilities’ are actually diseases in a conventional sense (Oliver, 1986) – this has important implications for a theory of enhancement if non-enhanced individuals are regarded as relatively disabled compared to enhanced individuals.

Appendix B. Additional material on Chapter 3

B.1. Protocol

B.1.1. Review question

The ultimate purpose of this systematic review is to generate a health economic theory of emerging human enhancement technologies. To support this aim, a review of normative literature on human enhancement topics is required, since it is expected that human enhancement will generate significant unique ethical challenges compared to conventional healthcare technology.

Therefore, the review question will be of the format proposed in McCullough et al. (2007): "In publicly funded healthcare systems, is it ethical to treat human enhancement technologies as presenting only 'generic' issues of resource allocation?"

B.1.2. Inclusion / exclusion criteria

Population

A publication will be included if it discusses the impact of a human enhancement technique on a population of healthy members of the public (adults or children). The stipulation that the population must be healthy is intended to exclude the considerable literature on enhancement-like techniques for improving the quality of life of unwell individuals (for example Bertolaso, Olsson, Picardi, and Rakela (2010), Fletcher (1995) or Grice and Kemp (2019)). This includes debate over whether certain categories of human variation count as an example of unwell-ness, for example whether short male children should be given human growth hormone to 'enhance' their height dimension (Murano, 2018).

The stipulation that the technique must apply to 'members of the public' will exclude publications focussing on specialised non-health applications, for example, human enhancement techniques for military applications (Parasidis, 2011), elite sporting competitions (Unal & Unal, 2004) and space exploration (Szocik & Braddock, 2019). The precise dividing line between a 'member of the public' and 'specific non-health application' is necessarily vague – doctors and university students are examples of roles which not all members of the public will have, but which feature extensively in the

human enhancement literature (Webb, Thomas, and Valasek (2010) and Singh, Bard, and Jackson (2014), respectively, for example). Therefore, inclusion and exclusion on these criteria is done on the basis of whether it is reasonable a publicly funded healthcare system would be the ultimate payer for this particular category of person (see intervention / comparison section below).

Intervention / Comparison

A publication will be included if its topic is any form of human enhancement that might be considered by a publicly funded healthcare system. This would include cognitive enhancement in a variety of different manifestations (intelligence, creativity, focus and so on) and physical enhancement in a variety of different manifestations (cosmetic enhancement, general improvement in biological human systems and so on), but explicitly exclude forms of enhancement that would not be considered by a publicly funded system, described in Chapter 2. In addition, the following exclusions are made in order to focus the review on the key question of relevance to the research project:

1. Genetic enhancement (defined as the artificial alteration of somatic cell lines to produce desirable characteristics of the person being altered). Since the improvement to the cell line is heritable in a way no other enhancement technique can be, there is a complicated moral and economic codicil to evaluations of genetic manipulation because enhancements will persist throughout generations. This debate is orthogonal to debates about enhancement itself and so it is sensible to exclude genetic enhancement form the list of enhancements otherwise reviewed. Papers which comment on generic features of enhancement in the context of genetic enhancement will not be specifically excluded, but any arguments made which depend on this unique feature of genetic enhancement will not be taken forward out of the review.
2. Cloning (defined as making genetically identical copies of an individual for example to permit activities which would otherwise be impossible) since by the definitions set out in Chapter 2 and elsewhere the clone would not be an *enhanced* human, but rather another baseline human. Note therefore that techniques which both clone and enhance such as the

uploading of consciousness into an electronic medium (Hanson, 2016) would still be included since it is not cloning *per se* which is excluded but cloning with no additional enhancement

3. Moral enhancement (defined as making people behave better, for example oxytocin injections) since this is not healthcare except in an extremely indirect sense.
4. Life extension (defined as extending species typical life expectancy through reversing senescence rather than curing disease) since there already exists a framework for assessing the value for money offered by life extension technologies (i.e. the cost per QALY framework without modification).

Outcome

A publication will be included if it reports a normative argument highlighting a resource allocation issue, which goes beyond generic resource allocation issues inherent to any technology (an example of a generic resource allocation issue; if the supply of the technology is limited, we must determine who is eligible to obtain it). Publications which report empirical outcome measures will be excluded unless they also include a normative component. Publications which report theological reasoning (common in the human enhancement literature) will also be excluded since these are irrelevant to public body decision making in secular democracies.

Source

A publication will be included if it is written in English (due to language limitations of the reviewer) and intended for an academic audience (that is, a peer reviewed paper / book or official report from a government body). Human enhancement is a popular topic for informal blog posts from economists such as Hanson (2008) and Fuller (2017). A conventional literature review would recommend identifying these opinions and including them into the literature review (Montori, Swiontkowski, & Cook, 2003). However, there is a risk of including extremely weak or uninformed argumentation alongside contributions from professional ethicists without adequate disclaimers if this strategy is adopted – a particular risk given the intended audience for the review are not themselves professional

ethicists. This standard is consistent with other examples of systematic reviews in bioethics (McCullough et al., 2007).

B.1.3. Search strategy

Preliminary searches identified that directly relevant literature would likely be unavailable. For example, searches on PubMed for *"human enhancement" AND "health economics"* returns no hits, whereas *"human enhancement" AND "resource allocation"* returns one, which does not meet the inclusion criteria of this review. As described above, Wolbring et al. (2013) is a non-systematic review of peripherally relevant enhancement literature, and – on review of the included studies – none discuss resource allocation from an economic perspective. Consequently, an indirect approach will be used, identifying ethical argumentation about human enhancement with the intention of highlighting the health economic implications of claims made in these publications during data extraction. It is expected, therefore, that the review will trade sensitivity for specificity and the approach described below reflects this.

A synonym-based search strategy will be adopted, linking the concepts of 'ethics / justifiability' to concepts of 'human enhancement'. The search strings used are in Table 16. The 'ethics' terms are based on those used in Strech and Sofaer (2012), whereas the 'enhancement' terms are a combination of ordinary-language synonyms for enhancement such as 'augmentation' along with discipline-specific terms for enhancement (and related concepts such as transhumanism) taken from an introductory textbook on the issue (Agar, 2017). Consideration was given to using a pre-defined 'bioethics' search string (Kennedy Institute of Ethics, 2019), but this approach lacked sensitivity for terms likely to appear in ethical argumentation about human enhancement and nowhere else (such as "liberal eugenics"), consistent with the predefined decision to trade sensitivity for specificity where possible.

Table 16 – Search terms used in synonym-based search

Concept	Synonym set 1	Synonym set 2	Synonym set 3
Ethics	**Generic terms for ethics:** 1. Ethics (ethical, unethical, ethically, ethicality)	**Terms likely to appear in ethical argumentation:** 1. Acceptability / Acceptance 2. Equality / Equity	**Ethical frameworks:** 1. Consequentialism 2. Utilitarianism 3. Deontology 4. Virtue Ethics

	2. Morality (moral, immoral, immorality, "morally right", "morally wrong")	3. Fairness / Fair 4. Genocide / ethnocide / eugenics / liberal eugenics 5. Beneficence 6. Autonomy 7. Justice / just 8. "Best interest(s)" 9. Justified / justifiability	5. Contractarianism
Enhancement	**Generic terms for enhancement:** 1. (Human) enhancement 2. Transhuman(ism/ist) 3. Posthuman(ism/ist) 4. Futurism(/ist)	**Potential routes to enhancement:** 1. Gene(tic) modification / gene therapy 2. Bioprostheses 3. Cyborg(ism/ist) 4. Wirehead 5. ((Whole/Partial) Brain) Emulation	**Subfields of enhancement:** 1. Cognitive enhancement / augmentation / modification (E/A/M) 2. Intellectual E/A/M 3. Physical E/M* 4. Mood E/A/M 5. Creativity E/A/M

Note that a 'physical' is American English for a medical examination – many papers describe methods to 'augment' the standard medical examination, and so this term was not searched due to very low sensitivity

Searching multiple databases is good practice to ensure that any inadequacies of a search string are compensated for by differing indexing strategies between databases (Petticrew & Roberts, 2006). Strech and Sofaer (2012) suggest there is no well-established strategy for which databases to search in a bioethics setting, and so a mix of conventional biomedical databases and smaller more focused ethical databases will be used. Larger databases such as PubMed, EMBASE and CINAHL will be used to identify conventional biomedical literature with ethical considerations, whereas more philosophy-specific databases such as JSTOR and ETHXWeb will be used to identify publications not indexed by biomedical databases. In addition, legal databases such as Westlaw International will be searched; the regulation of human enhancement is of interest to legal ethicists, and this may add depth to the search. Table 17 gives a list of all databases to be searched.

Table 17 – Databases to be searched

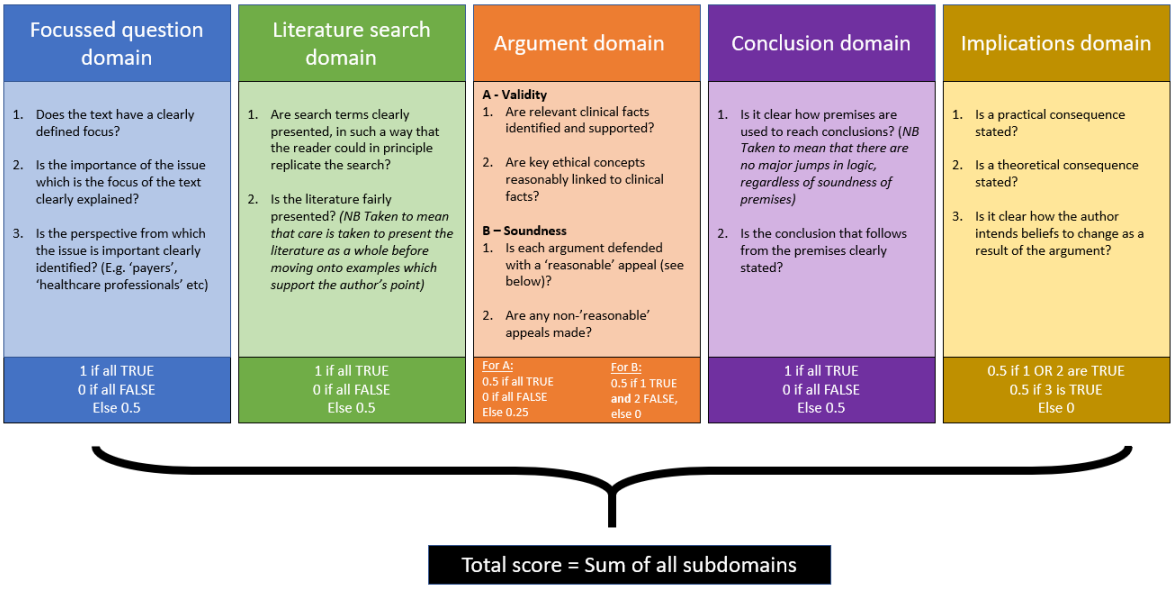
Biomedical	1. MedLine 2. PubMed 3. EMBASE 4. CINAHL
Ethics	5. ETHXWeb 6. JSTOR
Law	7. Westlaw International 8. Google Scholar

Grey literature will be searched by employing 'citation chaining' (Sayers, 2008; Talja et al., 2007).

B.1.4. Quality assessment

Quality assessment will be undertaken as described in McCullough et al. (2004). Five domains are assessed, with each domain receiving a score of '1' if it is entirely present, '0' if it is entirely absent and '0.5' if it is partially present. The original McCullough publication is unclear about exactly how each domain is to be scored and the constituents of each subdomain, therefore a more precise description of how scores are assigned to domains in this review is given in Figure 44.

Figure 44 – Relationship between domains, subdomains and overall score in quality assessment in the review, based on McCullough et al. (2004)



The overall score for a paper will be the sum of the scores awarded in each individual domain. Therefore, the maximum score for quality assessment of a paper is 5, indicating that the paper has met the minimum standard in all five domains. No quality cut-off will be used to include/exclude papers – the scores are included as an 'at a glance' guide to decision makers when assessing the quality of argumentation.

B.1.5. Data synthesis

When reporting results, a range of manuscript groupings will be presented based on different levels of analysis. Manuscripts will be grouped first by broad topic or theme regarding human enhancement (for example, 'cognitive enhancement' or 'cosmetic enhancement'), then included papers will be further subgrouped by specifics of the conclusion (for example; always right, right in some

circumstances or for some purposes, requires regulation etc). Formal argument-mapping software will be used if the data are suitable and it is necessary to do so to capture the dialogic nature of the bioethics literature. The intended audience for this review is policymakers, and therefore specific attention will be paid to arguments with an economic component, or which are relevant to current ongoing debates in health economics.

These arguments will then be compared, with similarities and differences discussed. Care will be taken to observe whether higher-quality papers tend to group on one side of the argument, and a detailed discussion on what biases might result to the overall literature base will be undertaken if this result is found. Collected information will also be used to assess whether there have been temporal changes to authors' position on human enhancement. Any arguments which can be linked to relevant debates in health economics will be so linked, to explicitly draw this aspect of the review out.

B.2. Search Strings

B.2.1. Pubmed

Searched 07/04/20

Search	Search string	Hits
Terms related to morality		
Generic terms for ethics		
1	(biomedical ethics[MeSH Terms]) OR *ethic*[Title/Abstract]	134697
2	(morality[MeSH Terms]) OR *moral*	211133
3	1 OR 2	280436
Terms likely to appear in ethical arguments		
4	((“genocide”) OR “ethnocide”) OR “eugenics”	6166
5	Beneficence	4684
6	Autonomy	47954
7	“Best interest”	1551
8	Justi*	128950
9	Fairness	3684
10	Equity	29092
11	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	210551
Ethical frameworks		

12	((((consequentialism[MeSH Terms]) OR utilitarianism[MeSH Terms]) OR deontological ethic[MeSH Terms]) OR virtue[MeSH Terms]) OR "contractarian*"	4230
13	3 OR 11 OR 12	446839
Terms related to human enhancement		
Generic terms for enhancement		
14	"human enhancement"	165
15	(biomedical enhancement[MeSH Terms]) OR enhancement[MeSH Terms]	2220
16	posthuman*	193
17	transhuman*	281
18	14 OR 15 OR 16 OR 17	2698
Potential routes to enhancement		
19	bioprostheses[MeSH Terms]	11489
20	cyborg*	130
21	wirehead	0
22	"brain 167mulate*"	6
23	enhancement, genetic[MeSH Terms]	1664
24	19 OR 20 OR 21 OR 22 OR 23	13288
Subfields of enhancement		
25	(("167mula* enhancement") OR "167mula* modification") OR "167mula* augmentation"	3807
26	(("cognitive enhancement") OR "cognitive modification") OR "cognitive augmentation"	1190
27	(("mood enhancement") OR "mood augmentation") OR "mood modification"	8905
28	(("creativity enhancement") OR "creativity augmentation") OR "creativity modification"	385
29	("physical modification") OR "physical enhancement"	225
30	25 OR 26 OR 27 OR 28 OR 29	14457
31	18 OR 24 OR 30	28698
Full search string		
32	13 AND 31	1564

B.2.2. MedLine

Searched 07/04/20

(((((((("human enhancement") OR transhuman*) OR posthuman*) OR ((biomedical enhancement[MeSH Terms]) OR enhancement[MeSH Terms]))) OR (((((bioprostheses[MeSH

Terms]) OR cyborg*) OR wirehead) OR “brain 168mulate*”) OR enhancement, genetic[MeSH Terms])) OR (((((((“physical modification”) OR “physical enhancement”)) OR (((“creativity enhancement”) OR “creativity augmentation”) OR “creativity modification”)) OR (((“mood enhancement”) OR “mood augmentation”) OR “mood modification”)) OR (((“cognitive enhancement”) OR “cognitive modification”) OR “cognitive augmentation”)) OR (((“intellect* enhancement”) OR “intellect* modification”) OR “intellect* augmentation”)))) AND ((((((((((((“genocide”) OR “ethnocide”) OR “eugenics”)) OR beneficence) OR autonomy) OR “best interest”) OR justi*) OR fairness) OR equity)) OR (((((consequentialism[MeSH Terms]) OR utilitarianism[MeSH Terms]) OR deontological ethic[MeSH Terms]) OR virtue[MeSH Terms]) OR “contractarian*”)) OR (((((morality[MeSH Terms]) OR *moral*)) OR ((biomedical ethics[MeSH Terms]) OR *ethic*[Title/Abstract]))))

74 hits

B.2.3. EmBase

Searched 07/04/20

Search	Search string	Hits
Terms related to morality		
Generic terms for ethics		
1	Bioethics/ or medical ethics/ or ethics/	174581
2	Morality/	35483
3	1 OR 2	195658
Terms likely to appear in ethical arguments		
4	Genocide/	416
5	Eugenics/	153
6	Ethnocide.mp.	9
7	Beneficence/	3622
8	Personal autonomy/	13453
9	“Best interest”.mp.	2028
10	Justice/	5979
11	Fairness.mp/	4058
12	Health equity/	2789
13	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	30055
Ethical frameworks		
14	utilitarianism.mp. or consequentialism.mp. or virtue ethics.mp. or deontology/ or	1894

	contractarianism.mp.	
15	3 OR 13 OR 14	215725
Terms related to human enhancement		
Generic terms for enhancement		
16	Human enhancement.mp.	157
17	Biomedical enhancement/	164
18	Posthuman.mp.	60
19	Transhuman.mp.	12
20	14 OR 15 OR 16 OR 17	355
Potential routes to enhancement		
21	Bioprosthesis/	6942
22	Cyborg.mp.	115
23	Wirehead.mp.	0
24	Brain emulation.mp.	5
25	Genetic enhancement/	977
26	21 OR 22 OR 23 OR 24 OR 25	8039
Subfields of enhancement		
27	(« intelligence enhancement » or « intelligence modification » or « intelligence augmentation »).mp.	9
28	(“cognitive enhancement” or “cognitive modification” or “cognitive augmentation”).mp.	1609
29	(“mood enhancement” or “mood modification” or “mood augmentation”).mp.	173
30	(“creativity enhancement” or “creativity modification” or “creativity augmentation”).mp.	8
31	(“physical enhancement” or “physical modification”).mp.	266
32	27 OR 28 OR 29 OR 30 OR 31	2055
33	20 OR 26 OR 32	10383
Full search string		
34	15 AND 33	703

B.2.4. CINAHL

Searched 07/04/20

Search	**Search string**	**Hits**
Terms related to morality		
Generic terms for ethics		
1	(MH “Bioethics”) OR (MH “Ethics, Medical”) OR (MH “Ethics”)	25437
2	Morality/	1644
3	1 OR 2	26800
Terms likely to appear in ethical arguments		

4	Genocide	315
5	Eugenics	314
6	Equality	4758
7	Beneficence	2404
8	Personal autonomy	98
9	“Best interest”	905
10	Ethnocide	4
11	Fairness	1889
12	Equity	9320
13	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	19339
Ethical frameworks		
14	Utilitarianism or consequentialism or deontological ethics or virtue ethics or contractarianism or contractarian ethics	841
15	3 OR 13 OR 14	45400
Terms related to human enhancement		
Generic terms for enhancement		
16	“Human enhancement”	89
17	(MH “Biomedical Enhancement”)	62
18	posthuman	36
19	transhuman	3
20	16 OR 17 OR 18 OR 19	176
Potential routes to enhancement		
21	Bioprostheses	207
22	Cyborg	68
23	Wirehead	0
24	“Brain emulation”	1
25	“Genetic enhancement”	59
26	21 OR 22 OR 23 OR 24 OR 25	335
Subfields of enhancement		
27	intelligence enhancement OR intelligence modification OR intelligence augmentation	533
28	(“cognitive enhancement” or “cognitive modification” or “cognitive augmentation”).mp.	1626
29	(“mood enhancement” or “mood modification” or “mood augmentation”).mp.	669
30	(“creativity enhancement” or “creativity modification” or “creativity augmentation”).mp.	62
31	(“physical enhancement” or “physical modification”).mp.	6502
32	27 OR 28 OR 29 OR 30 OR 31	8959
33	20 OR 26 OR 32	9435
Full search string		
34	15 AND 33	161

B.2.5. JSTOR

Searched 07/04/20

"((((“human enhancement”) OR (“biomedical enhancement”))”

Results limited to journal articles tagged as having the following subjects:

1. Biological Sciences – 40 hits
2. Economics – 4 hits
3. Health Policy – 43 hits
4. Health Sciences – 97 hits
5. Public Health – 3 hits

B.2.6. EthxWeb

Searched 07/04/20

1. “Human enhancement” – 32 hits
2. Posthuman – 9 hits
3. Transhuman – 3 hits
4. “Cognitive enhancement” – 19 hits
5. All other combination of X enhancement / modification / augmentation – 1 hit

B.2.7. Westlaw

Searched 07/04/20

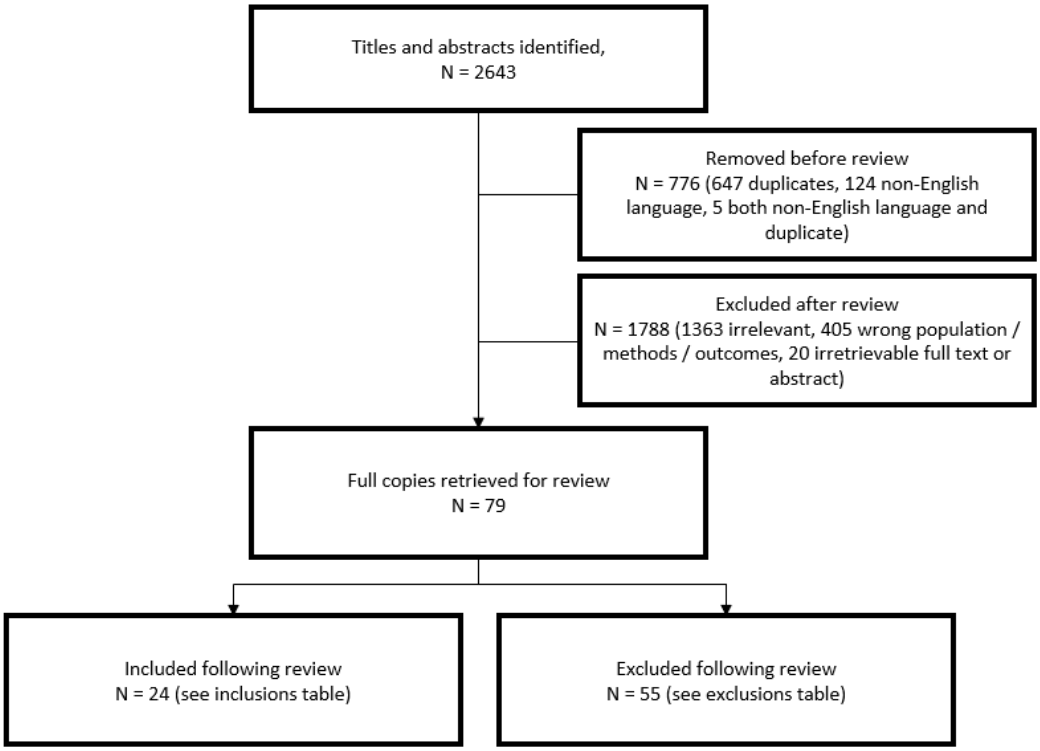
- “Human enhancement” – 25 hits
- Transhuman – 24 hits
- Posthuman – 19 hits

B.2.8. Google Scholar (case law only)

Searched 07/04/20

- “Human enhancement” – 3 hits
- Transhuman -spirit – 0 hits
- Posthuman -spirit – 0 hits

B.3. PRISMA flowchart



B.4. Included studies

Bibliographic details				Scoring domains*						Conclusions		
Title	**Authors**	**Date**	**Journal**	**1**	**2**	**3**	**4**	**5**	**Total**	**Position taken**	**Other positions considered**	**Categorisation of position**
A Responsibility to Chemically Help Patients with Relationships and Love?	Enck, Gavin G. Ford, Jeanna	2015	Cambridge Quarterly of Healthcare Ethics	0.5	0	0.75	0.5	1	**2.75**	Clinicians should use their judgement		Gatekeeper
Cognitive Enhancement and Beyond: Recommendations from the Bioethics Commission.	Allen, Anita L. Strand, Nicolle K.	2015	Trends in Cognitive Sciences	0.5	0	0	0.5	1	**2**	Ensure equitable access to certain enhancements		Distributive justice
Cognitive enhancement in neurological and psychiatric disorders using transcranial magnetic stimulation (TMS): A review of modalities, potential mechanisms and future implications.	Kim, Tammy D. Hong, Gahae Kim, Jungyoon Yoon, Sujung	2019	Experimental Neurobiology	1	1	0.75	0.5	1	**4.25**	Not clearly explained, but clear worry that it can reinforce socioeconomic class gap between those who can and cannot access enhancement		Distributive justice
Cognitive enhancement, cheating, and accomplishment.	Goodman, Rob	2010	Kennedy Institute of Ethics journal	1	0	0.5	1	1	**3.5**	Purpose of enhancement is important – should only enhance traits which are cooperatively aligned		Benefit society
Cognitive enhancement, rational choice and justification.	Veljko Dubljevic	2013	Neuroethics	1	0.5	0.75	1	0.5	**3.75**	Unclear	Laissez faire Medical professionals act as 'gate-keeper' Redistributive taxation Regulatory Authority for Cognitive Enhancements (RACE) Economic Disincentives Model	Unclear
Cognitive enhancement: Methods, ethics, regulatory challenges.	Bostrom, Nick Sandberg, Anders	2009	Science and Engineering Ethics	0.5	0.5	1	1	0.5	**3.5**	Unclear	Laissez faire below some level of risk (e.g. the risk of horseback riding) Enhancement licensing (non-RACE model) Subsidise enhancements	Unclear

Bibliographic details				Scoring domains*						Conclusions		
Title	**Authors**	**Date**	**Journal**	**1**	**2**	**3**	**4**	**5**	**Total**	**Position taken**	**Other positions considered**	**Categorisation of position**
Cognitive regeneration or enhancement: the ethical issues.	Chan, Sarah Harris, John	2006	Future Medicine	0.5	0	0.75	0.5	1	**2.75**	Legal but regulated market – allow pharma companies to prove efficacy / safety		No change
Developing public health approaches to cognitive enhancement: An analysis of current reports.	Outram, Simon M. Racine, Eric	2011	Public Health Ethics	0.5	0.5	0.75	0.5	0.5	**2.75**	Public health approach – state should encourage enhancement	Laissez faire	Benefit society
Enhancement and Obsolescence: Avoiding an "Enhanced Rat Race".	Sparrow, Robert	2015	Kennedy Institute of Ethics Journal	1	0.5	1	1	1	**4.5**	Do not allow enhancements which will obsolete themselves rapidly (Keeler-Cretin paradox)		HTA impossible
Enhancement and the ethics of development.	Buchanan, Allen	2008	Kennedy Institute of Ethics Journal	0.5	0.5	0.5	1	1	**3.5**	Encouraged by state policies for positive externalities		Benefit society
Neuroenhancing public health.	Shaw, David	2014	Journal of Medical Ethics	0.5	0	0.25	0.5	1	**2.25**	Not appropriate for NHS to fund, but rather local government to avoid increasing health inequalities by benefitting cognitively advantaged more than disadvantaged		HTA impossible
Neurostimulation devices for cognitive enhancement: Toward a comprehensive regulatory framework.	Dubljević, V.	2015	Neuroethics	0.5	0.5	0.75	0	1	**2.75**	Economic Disincentives Model	Gatekeeper	Economic Disincentives Model
Not Just "Study Drugs" for the Rich: Stimulants as Moral Tools for Creating Opportunities for Socially Disadvantaged Students.	Ray, Keisha Shantel	2016	The American Journal of Bioethics	0.5	0	1	0.5	1	**3**	Should be used to address socioeconomic inequalities		Distributive justice

Bibliographic details				Scoring domains*						Conclusions		
Title	**Authors**	**Date**	**Journal**	**1**	**2**	**3**	**4**	**5**	**Total**	**Position taken**	**Other positions considered**	**Categorisation of position**
One danger of biomedical enhancements.	Rajczi, Alex	2008	Bioethics	1	0	0.5	1	1	**3.5**	Enhancement has specific features that mean it is likely to be overvalued in analysis		HTA impossible
Prohibition or Coffee Shops: Regulation of Amphetamine and Methylphenidate for Enhancement Use by Healthy Adults.	Veljko Dubljevic	2013	The American Journal of Bioethics	1	0.5	0.75	1	1	**4.25**	On a case-by-case basis, enhancement drugs could be made available for sale	Individual use encouraged (e.g. via government incentives) Individual use discouraged (e.g. via taxation) 'Soft drugs' approach – use is not prohibited, but sale is Enhancement licensing (non-RACE) Economic Disincentives Model – License as with other OTC medicines (e.g. from EMA) but also require license from users (like guns today)	N/A – position taken not relevant to HTA, but positions considered potentially relevant
Racist appearance standards and the enhancements that love them: norman daniels and skin-lightening cosmetics.	Lamkin, Matt	2011	Bioethics	0.5	0	1	1	1	**3.5**	Access to enhancement can create externality effects for non-enhanced		Benefit society
Regulation of devices for cognitive enhancement.	Maslen, Hannah Savulescu, Julian Douglas, Thomas Levy, Neil Kadosh, Roi Cohen	2013	The Lancet	0.5	0	0	1	1	**2.5**	Regulate tDCS devices as any other medical device		No change
Should we use Commitment Contracts to Regulate Student use of Cognitive Enhancing Drugs?	Danaher, John	2016	Bioethics	0.5	0.5	1	1	1	**4**	Voluntary 'commitment contracts' in student context		Gatekeeper (modified)

Bibliographic details				Scoring domains*						Conclusions		
Title	**Authors**	**Date**	**Journal**	**1**	**2**	**3**	**4**	**5**	**Total**	**Position taken**	**Other positions considered**	**Categorisation of position**
The Case of Pharmacological Neuroenhancement: Medical, Judicial and Ethical Aspects from a German Perspective.	Franke, Andreas G Northoff, Robert Hildt, Elisabeth	2015	Pharmacopsychiatry	0.5	0.5	0.5	0	0	**1.5**	Unclear	Laissez faire Prohibit 'Managed technological scepticism' – regulatory body 'Managed technological optimism' – used to benefit society	Unclear
Transcranial electrical stimulation for human enhancement and the risk of inequality: Prohibition or compensation?.	Lavazza, Andrea	2019	Bioethics	0.5	0.5	0.75	1	1	**3.75**	Compensation required for those who do not wish to use HE technology, but otherwise unregulated		Distributive justice
Untangling the Debate: The Ethics of Human Enhancement	Lin, Patrick Allhoff, Fritz	2008	Nanoethics	1	0.5	1	1	0	**3.5**	Should be regulated to ensure that the gap between advantaged and disadvantaged is not inequitably widened by enhancement technologies		Distributive justice
Principles of Justice as the Basis for Public Policy on Psychopharmacological Cognitive Enhancement	Dubljevic, Veljko	2012	Law, Innovation and Technology	1	0	0.75	1	1	**3.75**	Public funds should not be allocated to enhancement		HTA impossible
Toward a Legitimate Public Policy on Cognition-Enhancement Drugs	Dubljević, V.	2012	Neuroethics	0.5	0	0.75	1	1	**3.25**	Economic Disincentives Model	Gatekeeper	Economic Disincentives Model
Enhancing human capacities, Chapter 6 "The Social and Economic Impacts of Cognitive Enhancement"	Savulescu, Julian Ter Meulen, Ruud Kahane, Guy	2011	Published by John Wiley & Sons	0	0	1	0	1	**2**	There are direct personal / social economic benefits not usually accruing to medical interventions		Benefit society

**Scoring domains: 1 = Focussed question, 2 = Literature search, 3 = Argument, 4 = Conclusions, 5 = HTA application*

B.5. Excluded studies

Title	Authors	Date	Journal	Reason for exclusion
Be careful what you wish for? Theoretical and ethical aspects of wish-fulfilling medicine.	Buyx, Alena	2008	Med Health Care and Philos	Analysis of ethical issues, with no specific analysis relevant to health economics
Begging Important Questions About Cognitive Enhancement, Again.	Partridge, Brad Lucke, Jayne Finnoff, Jonathan Hall, Wayne	2011	The American Journal of Bioethics	Criticism of empirical work, with no specific analysis relevant to health economics
Better Parenting through Biomedical Modification: A Case for Pluralism, Deference, and Charity.	Wasserman, D.	2017	Kennedy Institute of Ethics Journal	Recommendation for parent-child relationship not relevant for government-citizen relationship
Beyond an Open Future.	Krutzinna, Jenny I.	2017	Cambridge Quarterly of Healthcare Ethics	No actionable economic tradeoff identified
Brain machine interface and human enhancement – An ethical review.	Jebari, Karim	2013	Neuroethics	No specific analysis relevant to health economics
Caffeine use by children: the quest for enhancement.	Bramstedt, Katrina A.	2007	Substance Use & Misuse	Concern that enhancement might undermine accomplishment (implication being that it should not be offered on NHS), but no specific analysis relevant to health economics
Clipping the angel's wings: why the medicalization of love may still be worrying.	Hauskeller, M.	2015	Cambridge Quarterly of Healthcare Ethics	No specific analysis relevant to health economics
Cognitive enhancement in children and adolescents: Is it in their best interests?.	Gaucher, N. Payot, A. Racine, E.	2013	Acta Paediatrica	Cognitive enhancement in otherwise healthy adolescents is simply not acceptable under any circumstances – no tradeoff identified and so no analysis relevant to health economics
Cognitive enhancement, lifestyle choice or misuse of prescription drugs? : Ethics blind spots in current debates.	Racine, Eric Forlini, Cynthia	2010	Neuroethics	No specific analysis relevant to health economics

Title	Authors	Date	Journal	Reason for exclusion
Cognitive enhancements in human beings.	Solomon, Louis M. Noll, Rebekka C. Mordkoff, David S.	2009	Gender Medicine	No specific analysis relevant to health economics
Considering the Causes and Implications of Ambivalence in Using Medicine for Enhancement.	Forlini, Cynthia Racine, Eric	2011	The American Journal of Bioethics	No specific analysis relevant to health economics
Contemplating cognitive enhancement in medical students and residents.	Webb, Jadon R Thomas, John W Valasek, Mark A	2010	Perspectives in biology and medicine	No specific analysis relevant to health economics
Cosmetic neurology: the controversy over enhancing movement, mentation, and mood.	Chatterjee, Anjan	2004	Neurology	No specific analysis relevant to health economics
Does Kantian Ethics Condone Mood and Cognitive Enhancement?.	Clewis, Robert	2017	Neuroethics	No specific analysis relevant to health economics
Enhancement technology and outcomes: what professionals and researchers can learn from those skeptical about cochlear implants.	Kermit, Patrick	2012	Health Care Analysis	Analysis is for individual clinicians and not healthcare system
Enhancement's place in medicine	Scripko, Patricia D.	2010	Journal of Medical Ethics	Analysis focusses on responses with no cost, and so not relevant for health economics
Ethical aspects of the abuse of pharmaceutical enhancements by healthy people in the context of improving cognitive functions.	Tomažič, T. Čelofiga, A. K.	2019	Philosophy, Ethics, and Humanities in Medicine	Analysis focusses on responses with no cost, and so not relevant for health economics
Ethical considerations in the framing of the cognitive enhancement debate.	Outram, Simon	2012	Neuroethics	No specific analysis relevant to health economics
Ethics for the pediatrician: the persuasion of enhancements in pediatrics.	Ferdinand Yates	2010	Pediatrics in Review	Explicitly about genetic ethics – should not have been included

Title	Authors	Date	Journal	Reason for exclusion
Examining reports and policies on cognitive enhancement: approaches, rationale, and recommendations.	Outram, Simon M. Racine, Eric	2011	Accountability in Research	Analysis focusses on responses with no cost, and so not relevant for health economics
Expectations regarding cognitive enhancement create substantial challenges.	Racine, E. Forlini, C.	2009	Journal of Medical Ethics	No actionable economic tradeoff identified – limited to "a balance between non-maleficence, justice and autonomy on this pressing social issue"
Focusing the Neuroscience and Societal Implications of Cognitive Enhancers.	Savulich, George Piercy, Thomas Brühl, AB Fox, Chris Suckling, John Rowe, James B O'Brien, John T Sahakian, Barbara J	2017	Clinical Pharmacology and Therapeutics	Actionable proposals of arguable health economic significance identified, but not relevant to HTA (eg form public-private partnership to investigate safety of monadafilin)
Forthcoming ethical issues in biological psychiatry.	Helmchen, Hanfried	2005	The World Journal of Biological Psychiatry	No specific analysis relevant to health economics
Humans should be free of all biological limitations including sex.	Hughes, James J.	2010	The American Journal of Bioethics	Not about enhancement in the conventional sense – should not have been included
Making all the children above average: ethical and regulatory concerns for pediatricians in pediatric enhancement research.	Berg, Jessica W Mehlman, Maxwell J Rubin, Daniel B Kodish, Eric	2009	Journal of Clinical Pediatrics	Actionable proposals of arguable health economic significance identified, but not relevant to HTA (eg allow participants in enhancement trials perpetual access to the technologies developed during those trials)
Male circumcision and the enhancement debate: harm reduction, not prohibition	Savulescu, Julian	2013	Journal of Medical Ethics	Analysis focusses on responses with no cost, and so not relevant for health economics

Title	Authors	Date	Journal	Reason for exclusion
Market stimulus and genomic justice: Evaluating the effects of market access to human germ-line enhancement.	Crozier, G. Hajzler, Christopher	2010	Kennedy Institute of Ethics Journal	Purely genomic – should not have been included
Moral and social reasons to acknowledge the use of cognitive enhancers in competitive-selective contexts.	Garasic, Mirko D. Lavazza, Andrea	2016	BMC Medical Ethics	Analysis focusses on responses with no cost, and so not relevant for health economics
Neuroethical issues in cognitive enhancement: Modafinil as the example of a workplace drug?.	Brühl, Annette B. D'angelo, Camilla Sahakian, Barbara J.	2019	Brain and Neuroscience Advances	No specific analysis relevant to health economics
Non-pharmacological Approaches to Cognitive Enhancement.	Dresler, Martin Sandberg, Anders Ohla, Kathrin Bublitz, Christoph Trenado, Carlos Mroczko-Wąsowicz, Aleksandra Kühn, Simone Repantis, Dimitris	2013	Neuropharmacology	No specific analysis relevant to health economics
On Love, Ethics, Technology, and Neuroenhancement.	Ferraro, David	2015	Cambridge Quarterly of Healthcare Ethics	Not about enhancement in the conventional sense – should not have been included
On the argument that enhancement is "cheating"	Schermer, M.	2008	Journal of Medical Ethics	Analysis focusses on responses with no cost, and so not relevant for health economics
Ought we to enhance our cognitive capacities?.	Tännsjö, Torbjörn	2009	Bioethics	No specific analysis relevant to health economics
Our Posthuman Future: Consequences of the Biotechnology Revolution, by Francis Fukuyama	Francis Fukuyama	2003	Published by Picador	No specific analysis relevant to health economics

Title	Authors	Date	Journal	Reason for exclusion
Parental enhancement and symmetry of power in the parent—child relationship	Gheaus, Anca	2016	Journal of Medical Ethics	No specific analysis relevant to health economics
Political Minimalism and Social Debates: The Case of Human-Enhancement Technologies.	Rodríguez-Alcázar, Javier	2017	Journal of Bioethical Inquiry	No specific analysis relevant to health economics
Primum non nocere or primum facere meliorem? Hacking the brain in the 21st century.	Borrione, Lucas Brunoni, Andre R.	2017	Trends in Psychiatry and Psychotherapy	No specific analysis relevant to health economics
Procreation machines: Ectogenesis as reproductive enhancement, proper medicine or a step towards posthumanism?	Eichinger, J. Eichinger, T.	2020	Bioethics	No specific analysis relevant to health economics
Regulating the Use of Cognitive Enhancement: an Analytic Framework.	Jwa, Anita	2019	Neuroethics	Considers coercive enhancement relationships (the government-individual relationship identified is the military), rather than the consent-based paradigm of NHS – wrong context for review
Reshaping human intelligence: The debate about genetic enhancement of cognitive functions.	Fuchs, Michael	2010	Human Reproduction & Genetic Ethics	No specific analysis relevant to health economics
Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation.	Hamilton, Roy Messing, Samuel Chatterjee, Anjan	2011	Neurology	No specific analysis relevant to health economics
Smart drugs for cognitive enhancement: Ethical and pragmatic considerations in the era of cosmetic neurology.	Cakic, V.	2009	Journal of Medical Ethics	Context not society perspective
Surgical body modification and altruistic individualism: a case for cyborg ethics and methods.	Frank, Arthur W	2003	J Qualitative Health Research	Not human enhancement in the conventional sense – should not have been included
tDCS for memory enhancement: Analysis of the speculative aspects of ethical issues.	Voarino, Nathalie Dubljevia, Veljko Racine, Eric	2017	Frontiers in Human Neuroscience	No specific analysis relevant to health economics

Title	Authors	Date	Journal	Reason for exclusion
The ethics of making the body beautiful: what cosmetic genetics can learn from cosmetic surgery.	Goering, Sara	2001	Philosophy and Public Policy Quarterly	Analysis focusses on responses with no cost, and so not relevant for health economics
The ethics of molecular memory modification	Hui, Katrina Fisher, Carl E.	2015	Journal of Medical Ethics	No specific analysis relevant to health economics
The future of psychopharmacological enhancements: Expectations and policies.	Schermer, Maartje Bolt, Ineke Jongh, Reinoud Olivier, Berend	2009	Neuroethics	No specific analysis relevant to health economics
The medicalization of love and narrow and broad conceptions of human well-being.	Nyholm, Sven	2015	Cambridge Quarterly of Healthcare Ethics	No specific analysis relevant to health economics
Thinking across species – A critical bioethics approach to enhancement.	Twine, Richard	2007	Philosophy of Medical Research and Practice	Wrong population – focusses on animals
Towards a smart population: A public health framework for cognitive enhancement.	Lucke, Jayne Partridge, Brad	2013	Neuroethics	Argues that public health interventions are more effective than human enhancement at the moment, but does not have relevance to human enhancement policy as not relevant to NHS context
Transcranial electrical stimulation to enhance cognitive performance of healthy minors: A complex governance challenge.	Schuijer, Jantien W. De Jong, Irja M. Kupper, Frank Van Atteveldt, Nienke M.	2017	Frontiers in Human Neuroscience	Although an analysis with health economic features is identified, tradeoffs are not sufficiently well specified to make economic analysis
Trivial Love.	Macgregor, Oskar	2015	Cambridge Quarterly of Healthcare Ethics	No specific analysis relevant to health economics

Title	Authors	Date	Journal	Reason for exclusion
True and false concerns about neuroenhancement: a response to 'Neuroenhancers, addiction and research ethics', by D M Shaw.	Heinz, Andreas Kipke, Roland Müller, Sabine Wiesing, Urban	2014	Journal of Medical Ethics	No specific analysis relevant to health economics
Unrequited: neurochemical enhancement of love.	Bamford, Rebecca	2015	Cambridge Quarterly of Healthcare Ethics	No specific analysis relevant to health economics
What is morally salient about enhancement technologies?	Pols, Auke J. K. Houkes, Wybo	2011	Journal of Medical Ethics	Discussion about different categories of human enhancement without conclusion about how it might affect policy, rather than analysis of health economic factors of that policy

Appendix C. Additional material on Chapter 4

C.1. Design of Simulation Model

C.1.1. Parameters

The purpose of the simulation model is to duplicate the conditions that would face a new technology being assessed by a health technology appraisal body such as NICE, and then identify if any combination of hypothetical conditions and technologies would cause a conflict with other health system objectives.

The model is a state-transition discrete-time model built in Microsoft Excel, with a step length of one year and a time horizon of 100 years. It simulates a cohort of 100 patients who receive a hypothetical enhancement technology or remain on BSC. 100 patients is justified as although convergence occurs almost instantaneously in the base case (Figure 45), because the eventual role of the model will be to simulate more unstable structural assumptions 100 patients offered a good balance between speed of execution and convergence in highly unstable scenarios (Figure 46)

Figure 45 – Convergence diagram for base case model output

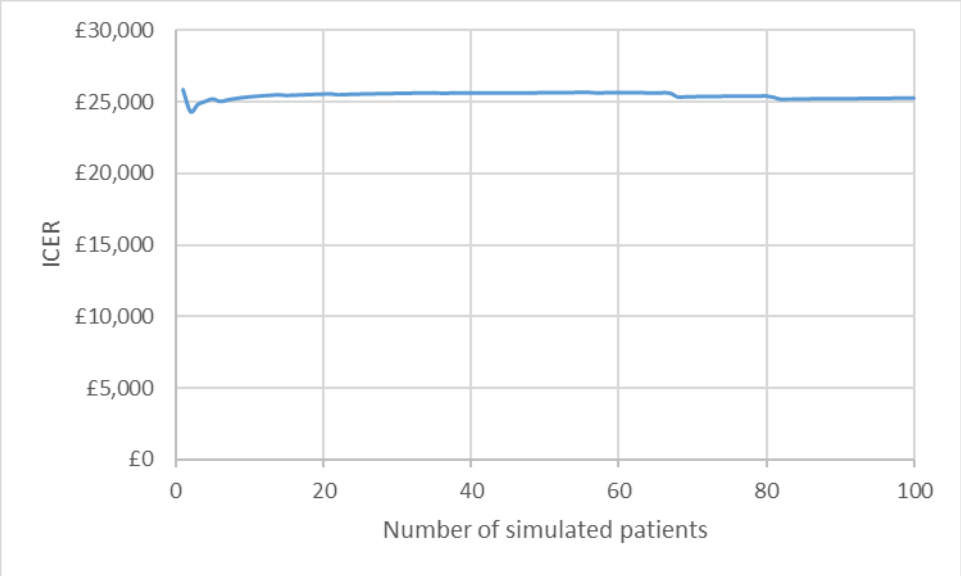
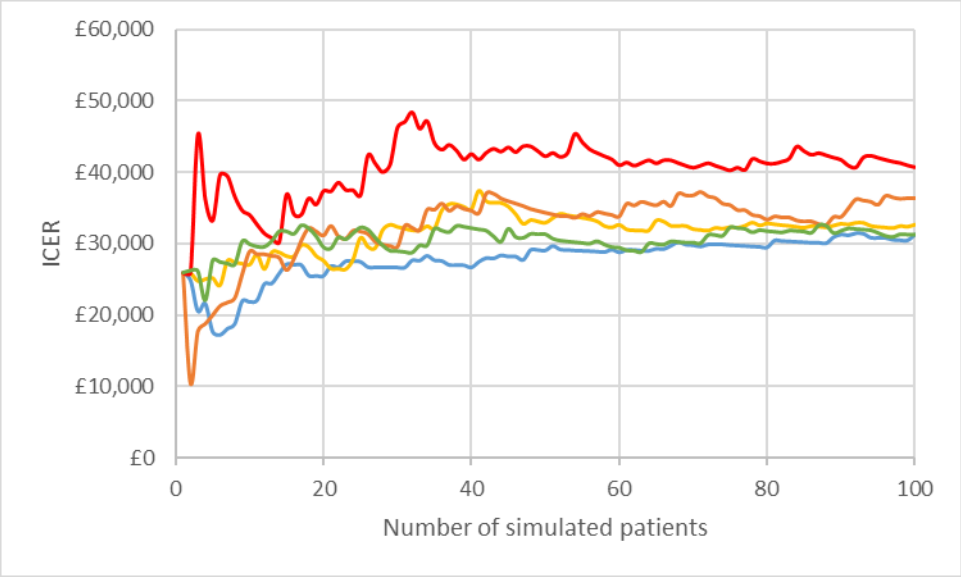


Figure 46 – Convergence diagram for example unstable case model output



Parameters were highly flexible, and reflected the research goals of exploring a significant fraction of the possible enhancement-space. Table 18 demonstrates the parameterisation of the model in its 'default' deterministic state (note that some additional parameters relating to population and intervention setup have been excluded for brevity, as they are discussed below).

Table 18 – Default parameterisation of the model

Parameter	Default Value	Distribution	Lower Error	Upper Error
UK Population	68,000,000	None	N/A	N/A
NHS Budget (£billion)	140	None	N/A	N/A
Population eligible	1.23%	Gamma	16.81	0.00073171
Starting age	18	Uniform	18	70
Cost age dep?	No	None		
QALY age dep?	Yes	None		
QoL Taper	50.00%	Uniform	0	100
Discount unenhanced costs	3.50%	Scenario	N/A	N/A
Discount unenhanced QALYs	3.50%	Scenario	N/A	N/A
Discount enhanced costs	3.50%	Scenario	N/A	N/A
Discount enhanced QALYs	3.50%	Scenario	N/A	N/A
Unenhanced Base NHS Costs	2,059	Gamma	1.864878618	1103.998678
Unenhanced Base Societal Costs	0	None	N/A	N/A
Unenhanced QALYs	0.86	Normal	0.23	N/A
Unenhanced Mortality HR	1.00	None	N/A	N/A
Enhanced Base NHS Costs	1,716	Gamma	1.295054596	1324.798414
Enhanced Base Societal Costs	0	None	N/A	N/A
Enhanced QALYs	1.20	Normal	0.23	N/A
Enhanced Mortality HR	0.80	None	N/A	N/A
Diseased Base NHS Costs	4,118	Gamma	7.459514472	551.9993392

Diseased Base Societal Costs	0	None	N/A	N/A
Diseased QALYs	0.62	Normal	0.23	N/A
Diseased Mortality HR	1.20	None	N/A	N/A
Enhanced Disease Base NHS Costs	2,059	Gamma	1.864878618	1103.998678
Enhanced Disease Base Societal Costs	0	None	N/A	N/A
Enhanced Disease QALYs	0.86	Normal	0.23	N/A
Enhanced Disease Mortality HR	1.00	None	N/A	N/A
Posthuman Base NHS Costs	1,716	Gamma	1.295054596	1324.798414
Posthuman Base Societal Costs	0	None	N/A	N/A
Posthuman QALYs	0.10	Normal	0.026744186	N/A
Posthuman Mortality HR	0.01	None	N/A	N/A
Enhancement posology	Branded pharmaceutical*	Scenario	N/A	N/A
Technology scenario	Standard*	Scenario	N/A	N/A
Enhancing population	Standard*	Scenario	N/A	N/A
Slowing value	0.1	Beta	89.9	809.1
Disease incidence	0.1	Beta	94.95	1804.05
Disease cure prob	0.3	Beta	74.75	224.25
Enhanced Disease incidence	0.1	Beta	94.95	1804.05
Enhanced Disease cure prob	0.3	Beta	74.75	224.25
Stasis reversion prob	0.1	Beta	89.9	809.1
Posthuman transition prob	0.1	Beta	89.9	809.1

Owing to the information uncovered in the Literature Review in Chapter 3, it was considered more appropriate to vary three key parameters with scenario analysis rather than a continuously varying underlying parameter, marked with an asterisk. This ‘structural probabilistic sensitivity analysis’ is described in NICE (2022) and represents the cutting-edge of uncertainty analysis. The three parameters so effected are the posology of the enhancement (affecting costs), the mechanism of action of the enhancement (affecting transition probabilities) and society’s response to that enhancement (affecting costs and QALYs). In addition, discounts rates are varied as part of a scenario, but this is more of an aesthetic choice to represent the ongoing debate in e.g. Briggs et al. (2006) rather than a requirement of good modelling practice. Details on the ‘posology’, ‘population’ and ‘technology’ scenarios are given in Table 19, Table 20 and Figure 47 respectively.

Table 19 – Options for ‘posology’ scenarios

Posology	One-off cost	Ongoing cost	Reference

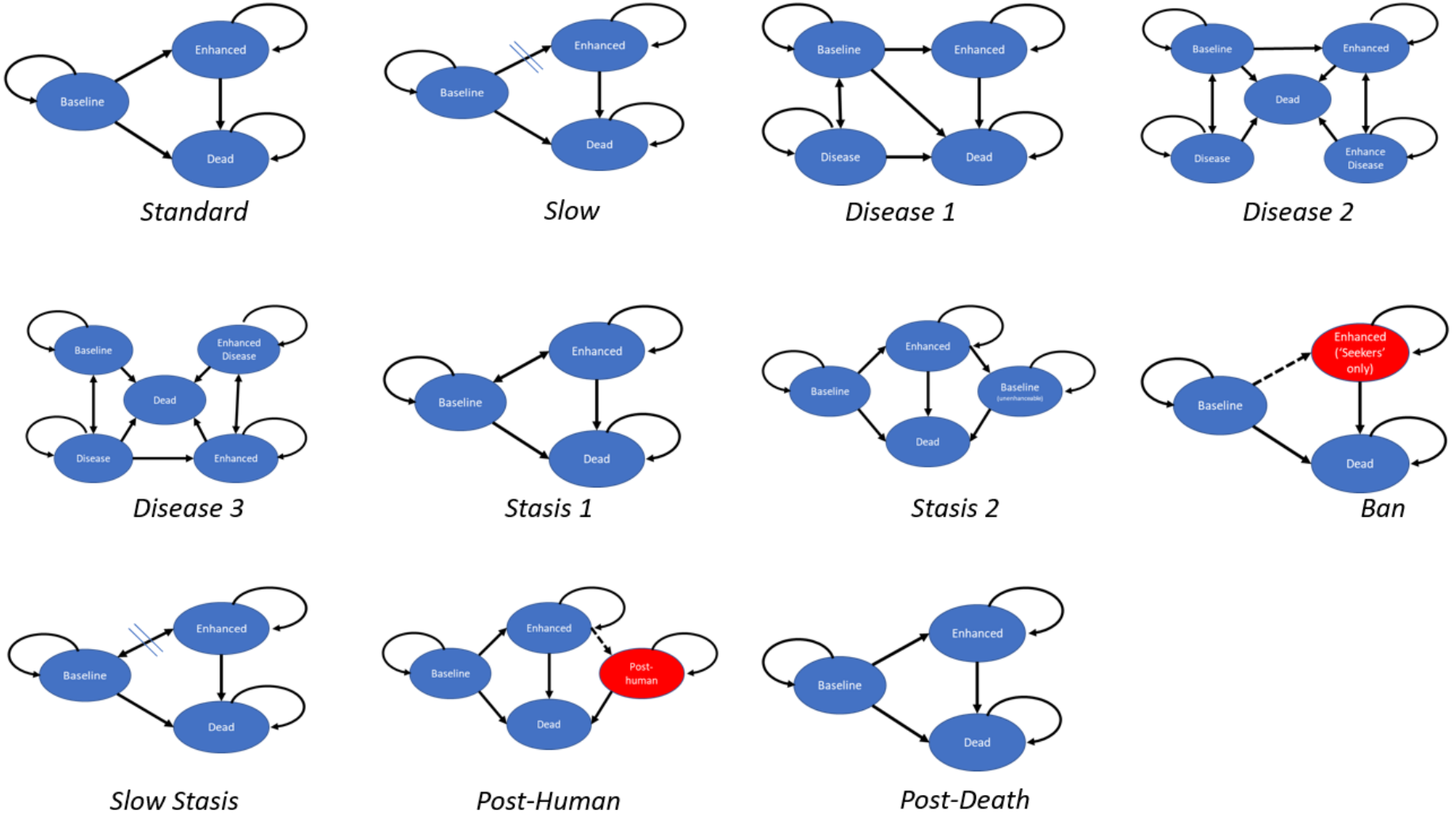
Vaccine	£3	£0	*Cost of course of AZ COVID vaccine, https://www.hln.be/binnenland/zoveel-gaan-we-betalen-voor-de-coronavaccins-staatssecretaris-zet-confidentiele-prijzen-per-ongeluk-online~a3dceef4/180355293/*
Generic pharmaceutical	£0	£101	*BNF Category M prices for Paracetamol 500mg capsules, cost of £4.63 for 100 tablets assuming 6 tablets/day available https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff/drug-tariff-part-viii accessed 19/12/21. Selected on the basis of being a common generic pharmaceutical.*
Branded pharmaceutical	£0	£9,146	*NHS High Cost Drug Tariff for Adalimumab 40mg/0.4ml solution for injection pre-filled syringes, cost of £357 for two pre-filled syringes, assuming 40mg weekly, available at https://www.drugtariff.nhsbsa.nhs.uk/#/00812617-DC/DC00812303/Part%20VIIIA%20products%20A accessed 19/12/21. Selected on the basis of being the highest budget impact branded pharmaceutical for the NHS.*
Minor surgery	£157	£2	*NHS Reference Costs for JC43C, Minor Skin Procedure. Ongoing costs assumed to be 1% of one-off costs. Selected as the most common NHS surgical operation. Available at https://www.england.nhs.uk/national-cost-collection/#ncc1819, accessed 19/12/21*
Major surgery	£94,301	£943	*NHS Reference Costs for ED04Z, Complex Heart Transplant. Ongoing costs assumed to be 1% of one-off costs. Selected as the most expensive NHS surgical operation that was not paediatric. Available at https://www.england.nhs.uk/national-cost-collection/#ncc1819, accessed 19/12/21*
Ongoing surgery	£94,301	£9,146	*Assumption - equivalent of 'Major Surgery' in first year and then 'Branded Pharmaceutical' every year thereafter*

Table 20 – Options for 'population' scenarios (the lay-language 'Description' is cashed out as multiplication factors in Table 18)

Archetype Number	Nickname	Description
1	Not eligible	*Used as generic 'non-enhancing' control group. Included only to allow easy manipulation of included population.*
2	Standard	*Will enhance ASAP to QoL >1 and then stay there until death*
3	Receptive	*Benefits more from being in the enhanced state, compared to population average, and more likely to remain enhanced*
4	Unreceptive	*Benefits less from being in the enhanced state, compared to population average, and less likely to remain enhanced*
5	Seeker	*Will enhance privately, regardless of availability on NHS*
6	Non-responder	*Cannot enhance, but ex ante doesn't know this (ie eligible for purpose of costs, but otherwise treated as 'Not Eligible'*
7	Healthy Base	*Healthier than average, so has better pre-enhancement costs and QALYs*
8	Unhealthy Base	*Sicker than average, so has worse pre-enhancement costs and QALYs*
9	Cheap Enhance	*Costs less to make and keep enhanced*
10	Cost Enhance	*Costs more to make and keep enhanced*

11	Ant	*Generate strong positive externalities through enhancement, based on average income tax paid in UK, sourced from https://www.statista.com/statistics/813239/average-income-tax-per-household-uk/ accessed 19/12/21*
12	Grasshopper	*Generate strong negative externalities through enhancement, based on average income tax paid in UK, sourced from https://www.statista.com/statistics/813239/average-income-tax-per-household-uk/ accessed 19/12/21*
13	Posthuman	*Will attempt to enter 'Posthuman' health state if it is offered (no other archetype will do this)*
14	Red Queen	*Utility is based on how many enhanced individuals there are, with diminishing returns*
15	Hipster	*Utility is based on how many enhanced individuals there are, with punishment for remaining unenhanced*
16	Luddite	*Enhancement lowers utility*
17	Disorganised	*Will take much longer to enhance than 'Standard'*

Figure 47 – Options for 'technology' scenarios



C.1.2. Validation

Briggs et al. (2006) identify four kinds of uncertainty relevant to economic modelling. Stochastic uncertainty will be resolved through running sufficient simulations to ensure accuracy. For parameter uncertainty, a reasonable underlying distribution will be used to investigate model sensitivity to this uncertainty (for example; if a parameter must take a value from [0, 1] then a beta distribution is appropriate, costs are usually handled with gamma distributions and so on). Heterogeneity and structural uncertainty are not relevant to this model since all technologies are hypothetical. More complex structural specifications are possible with the model (for example by using the unused health states or by toggling on transitions which are not available in the base case), but not thought necessary for validation.

Internal model validation will be conducted separately for the economic model and subsequent kNN reductions of the search space. The kNN algorithm can be tested by reducing the dimensionality of the problem to something human comprehensible, and ensuring that the model outputs sensible results (more formally, a Silhouette Coefficient can be calculated to ensure reasonable model fit in any number of dimensions (Rousseeuw, 1987)). The economic model can be compared against existing technology appraisals where a (non-enhancing) technology of a known ICER is run through the model and checked for consistency against these technologies, subject to expected small deviations due to slightly different model structures. Its validity can further be assessed using deterministic one-way sensitivity analysis, limiting parameter selection to those with known effects in real life and ensuring that changes to these parameters has plausible effects on outputs – for example, increasing the cost of a technology ought to increase the ICER of that technology relative to doing nothing. In addition to these formal tests of internal validity, the model will be made available to external experts upon request, including a expert health economist supervising the research, for comment and criticism.

External model validation will be conducted against the literature. That is, if an author has argued that X technology under Y conditions should produce Z effect, the model should find that effect under those conditions. If it does not, then it will be considered that the model may be suffering from a subtle error – especially if no other explanation for the discrepancy seems plausible.

C.1.3. Multiple Criteria Decision Analysis parameters

In Section 4.3.3.1 it is observed that the model requires Multiple Criteria Decision Analysis to function. Consequently, it is necessary to enumerate any decision element which should be replicated in the model.

Table 21 summarises these criteria, and which source prompted their inclusion. In essence, three sources are used:

- Clearly, decision criteria used in the model must at the least replicate important elements of NICE's social value judgements (NICE, 2008).
- There is a relatively extensive literature on MCDA simulations in a healthcare setting (especially Devlin and Sussex (2011); James et al. (2005)), and while this mostly overlaps with the NICE social value judgement, there are some novel elements which can be included for completeness
- Chapter 3 contains a literature review of potential failure states of enhancement regulation. By extracting the ethical insight in these documents, it is possible to include enhancement-specific criteria. Again, these broadly align with the NICE criteria.

In keeping with discussions in James et al. (2005), these criteria are subdivided into 'efficiency domains' and 'equity domains'

Table 21 – Factors of importance to HTA decision making

	Source			Notes
	NICE[1]	MCDA[2]	Lit Rev[3]	
Efficiency domains				
Cost-effectiveness	X	X	X	
Cost			X	Ultra-high cost interventions (such that a significant fraction of the NHS' budget is spent in one area) would likely be unacceptable to the general public, and would therefore violate this criteria
Effectiveness / Beneficence	X	X	X	Note that there is a subtle difference between improvements in health-related quality of life and improvements in subjective well-being (Devlin & Sussex, 2011); the simulation model cannot directly pick up on this distinction and assumes they are identical in practice

				Also note that we might regard a significant quality of life impact as different to merely improving health a little (James et al., 2005)
Externalities	X	X	X	Especially extreme negative social impact
Productivity		X		While economic productivity (and e.g. return to work) is described as a potentially relevant criteria for MCDA by Devlin and Sussex (2011), note that productivity is explicitly NOT considered by NICE in its Reference Case, due to a worry about unequal outcomes
'Rule of rescue'	X	X		When faced with a patient who can be treated, clinicians have an ethical obligation to disregard any efficacy concerns in the service of treating that patient. Note that NICE mention this rule only to disagree with it!
Impact of initial allocation of resources			X	Initial endowment of resources should not impact outcomes (for example, richer people should not be able to buy access into a better tier of treatment). Initial endowment of health resources is a special case discussed below.
Consistency	X			Any decision which clearly contradicts existing NICE Guidance should be rejected as creating ambiguity in the system
Coherence	?	?	?	Decisions which are incoherent, paradoxical or self-defeating should not be allowed
Equity domains				
Respect for autonomy	X		X	Patients ought to be offered choice in their care, where appropriate
Non-maleficence	X			Patients made worse off by an intervention (for example because of significant externality benefit such as described in the 'Transplant Problem' (Jarvis Thomson, 1985) would be considered a violation of this criteria
'Procedural' Justice	X		X	Making decisions in a fair and transparent way. Might also include what Devlin and Sussex (2011) describe as 'process of care' utility, which is satisfaction with the way care was delivered and decisions were taken.
'Horizontal' Justice	X	X		Identical patients should be entitled to identical treatment. This is especially relevant in the consideration of e.g. rare diseases
'Vertical' Justice	X	X	X	Treatments which reduce the overall level of health inequality are preferred over treatments which treat equally
'Rawlsian' Justice	X	X	X	The state of the worst off individual is the most morally relevant (see Rawls (1971) for the original analysis)
Abhorrence	?	?	?	Decisions which clearly violate some important moral precept not otherwise specified should not be allowed

1 – NICE (2008)
2 – Devlin and Sussex (2011); James et al. (2005)
3 – See Chapter 3 for full list of sources

However, not all of these can be operationalised in the model – for example outcomes which one author considers 'abhorrent' might be considered sound ethical judgement under uncertainty by another (see for example the exchange between Claxton & Culyer, 2006; Harris, 2005), and so there is no meaningful way to implement this judgement. Furthermore, there might be multiple ways to consider making a decision faced with the same information (should one look at the mean or median patient, for example). Therefore Table 22 summarises the implementation in the model. Where one parameter has multiple implementations it is considered a separate element of model dimensionality – therefore while we might commonly expect – for example – a close relationship between the incremental cost-effectiveness ratio and a binary classifier signifying whether the intervention is cost-effective or not, any scenarios leading to a systematic difference between these values will be captured.

Table 22 – Implementation of factors of importance to HTA decision making

Index	**Efficacy domains**	
0.0	Coherence	Incoherent decisions are impossible with an algorithmic approach, but nonsensical decisions (such as a requirement to divide by zero) will flag to the user that something unspecified went wrong with the process and therefore the result should be discarded. This value should be zero in all analysis presented in the thesis since incoherent decisions indicate that there is an error in the model
1.1a-1.4a	Cost-effectiveness 1	Expressed as a binary value (cost-effective or not), as per standard NICE methods (NICE, 2013). For the sake of simplifying an already challenging model specification, the conclusions of Devlin and Parkin (2004) will be assumed to be true – that is, in practice, NICE uses the higher end of the £20,000 - £30,000 threshold in making decisions (or perhaps a little higher), and therefore for the purposes of this modelling exercise NICE's threshold is assumed to be £30,000. Four relevant perspectives considered: • 1.1 – NHS / PSS • 1.2 – Societal • 1.3 – Therapy only ('capped' as 1 QALY / year) • 1.4 – Tapering approach
1.1b-1.4b	Cost-effectiveness 2	Expressed as a real number indicating the ICER, as per standard NICE methods (NICE, 2013). Four relevant perspectives considered: • 1.1 – NHS / PSS • 1.2 – Societal • 1.3 – Therapy only ('capped' as 1 QALY / year)

		• 1.4 – Tapering approach *Note that only one of 1.1a / 1.1b, 1.2a / 1.2b and so on should be toggled on in the model at any one time – otherwise they will autocorrelated with each other to the extent that kNN fails to find a target*
2.1	Cost	Expressed at the proportion of the NHS budget spent in whichever model year represents the peak spend for that cohort.
3.1	Effectiveness / Beneficence	Expressed as a binary value indicating an absolute QALY surplus of 12 QALYs or more generated by enhancement. This is in line with current NICE thinking regarding replacing the 'end of life' modifier with an 'absolute burden of disease' modifier, although note that this modifier would not apply to enhancements – it is just an indication of what NICE believe a 'meaningful' QALY impact might be. *Note that the new NICE methods (NICE, 2022), published after the analysis in this thesis was completed, actually gives the threshold for the most significant impact as 18 QALYs (although 12 is still used for when the impact begins to be important). This does not substantially affect analysis, as the NICE methods are only used as an indicative example of the kinds of methodology decisions made by HTA agencies*
	Productivity	*Arguably, the impact on quality of life of returning to work is captured in other domains, and the economic impact of returning to work can be considered a special kind of positive externality. Therefore, this is not implemented as a separate outcome to externality impacts*
	'Rule of rescue'	*It is not clear this can be meaningfully implemented*
	Impact of initial allocation of resources	*This is not implemented in the model, and is a limitation of the analysis*
	Consistency	*This will not be algorithmically assessed – see Section C.1.2 for information on how it will be assessed in practice*
	Equity domains	
3.2	Non-maleficence	Expressed as a ratio– what proportion of patients made worse off by implementing this technology? Note that this would not necessarily rule out implementing the technology – so-called 'south-west quadrant' technologies which both reduce QALYs and reduce spend in a cost-effective way are acceptable under NICE methods (NICE, 2013), and are controversial but well-studied in the broader health economics literature (Dowie, 2004). There are several examples of such technologies in practice, for example NICE TA433 (2017).
4.1	'Rawlsian' Justice	Expressed as an index – the ratio of QALY of worst-off 10% of population following intervention compared to the worst-off 10% of the control group

		Note that the single worst-off individual can sometimes lead to a degenerate solution (an individual who coincidentally dies in the first cycle of the model) and therefore the average well-being of the worst-off section of society is considered to avoid this. This is a weakness of simulation modelling, but the solution does not seem to undermine the concept of Rawlsian justice so is thought unlikely to materially impact outputs of the model.
4.2	'Vertical' Justice	Expressed as an index – the Slope Index of Inequality (SII) for the treatment group following intervention compared to the control group *Note that the SII is selected as a measure of vertical justice because it is easy to algorithmically implement and is used by healthcare authorities such as the WHO (World Health Organization, 2017) but it is acknowledged more complex measures might provide more reliable assessment of outcomes (Kjellsson, Gerdtham, & Petrie, 2015).*
4.3	'Horizontal' Justice	Expressed as an index – the Area Under the Cumulative Concentration Curve (AUCCC) for the treatment group following intervention compared to the control group (Tao, Henry, Zou, & Zhong, 2014)
	Respect for autonomy	*It is not clear this can be meaningfully implemented*
	'Procedural' Justice	*It is not clear this can be meaningfully implemented*
	Abhorrence	*It is not clear this can be meaningfully implemented*

These measures of equity mostly align with the definition of equity used in the main body of the thesis (that is, equity of health outcomes versus efficiency of the production of health). There are other definitions of equity which are highly relevant (for example we could look at equity of health inputs versus efficiency of delivery of a fixed quantity of health input) but for the purpose of modelling these distinctions are not so important since the concept of equity is so heavily abstracted away to allow for mathematical manipulation.

C.1.4. CHEERS statement

Table 23 – CHEERS statement

Section / item	**Location**
Title	N/A – Model is supplementary information to this thesis
Abstract	Section 4.3
Background and objectives	Chapter 2
Target population and subgroups	Section 4.4
Study perspective	Table 6 in Section 4.4
Comparators	Table 6 in Section 4.4

Time horizon	Table 6 in Section 4.4
Discount rate	Table 6 in Section 4.4
Choice of health outcomes	Table 6 in Section 4.4
Measurement of effectiveness	N/A
Measurement of preference-based outcomes	N/A
Estimating resources and costs	Table 6 in Section 4.4
Currency, price, date and conversion	Table 6 in Section 4.4
Choice of model	Section 4.3.1
Assumptions	Section 4.2
Analytical methods	Sections 5.3 and 5.4
Study parameters	Appendix C.1.1
Incremental costs and outcomes	Sections 4.5 and 4.6
Characterising uncertainty	Section 5.2
Characterising heterogeneity	Section 5.5
Study findings, limitations, generalisability	Section 5.6
Sources of funding	N/A
Conflicts of interest	N/A

C.2. Variations to 'Subversion' results

This subsection considers variations to the 'NHS Subversion' main results in Section 4.5, as part of the more general strategy of sensitivity analysis discussed in Appendix C.1.2.

C.2.1. 'Vaccine case'

Figure 48 – Base Case Variation 1 ('Vaccine case')

Results

Base case

Decision	APPROVE
ICER	DOMINANT

Societal case

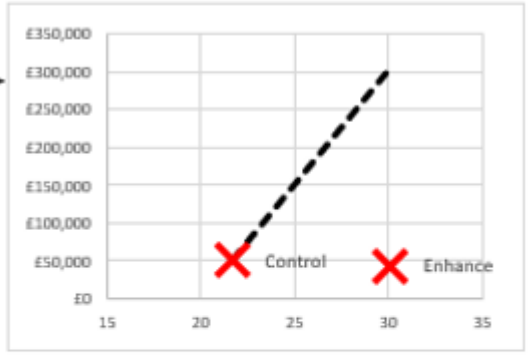
Decision	APPROVE
ICER	DOMINANT

Tapering case

Decision	APPROVE
ICER	DOMINANT

Capping case

Decision	APPROVE
ICER	DOMINANT



Equality outcomes	
NHS budget impact	1.02%
Probability harm	0.00%
Vertical equity index	0.72
H'zontal equity index	0.96
Rawlsian equity index	1.37

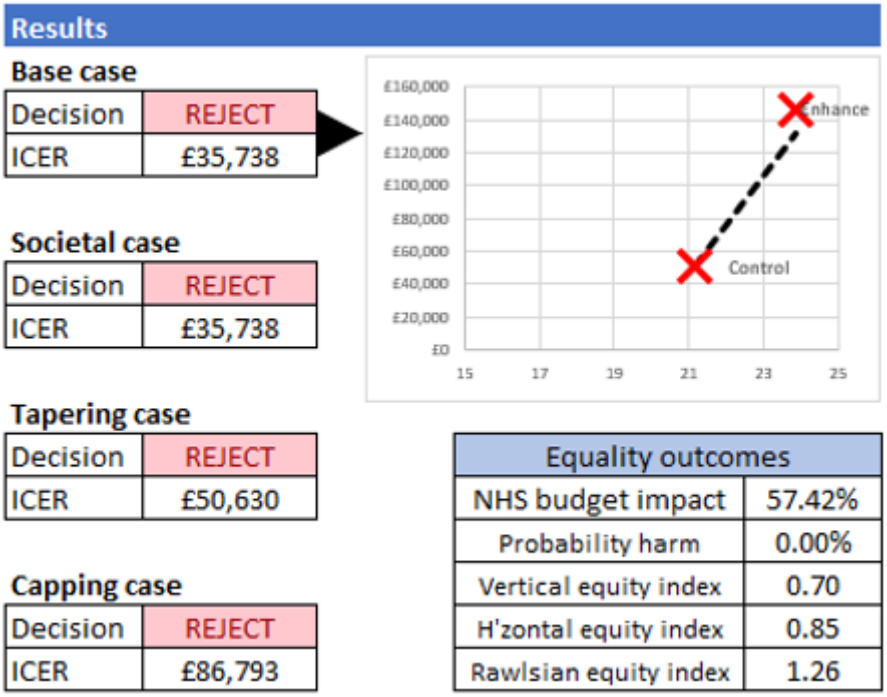
One slight oddity in the literature is the recurrent position that enhancements must adopt some particular modality – for example – "nanotechnology, biotechnology, information technology and cognitive science" interventions (Menuz et al., 2013) or "genetic engineering, pharmacology, bioengineering, cybernetics and nanotechnology" (Brey, 2009) interventions. This assumption is fairly strongly refuted in Chapter 2, but it may still be instructive to consider the full range of modalities in considering the Subverting effect.

In Figure 48, a variation to the Base Case is considered where a single one-off intervention is given which offers the same benefits as the Base Case and which lasts for the patient's lifetime. It is assumed that in the 'steady state' of this scenario approximately 1/80th of the population would be enhanced each year (for example enhanced at birth or on the 18th birthday). This scenario is approximately the situation that the NHS finds itself in with respect to vaccines (which are noted in Chapter 2 as an example of a 'proto-enhancement' which actually exists today). In this scenario the equity considerations are unchanged, but the budget impact is significantly smaller and the cost-effectiveness case significantly stronger. This demonstrates the stylised fact that there are some enhancement scenarios in which the case for the technology is so overwhelming that conventional

HTA processes will make the correct decision despite being ill-suited to make harder decisions at the margin.

C.2.2. 'Risky surgery' case

Figure 49 – Base Case Variation 2 ('Risky surgery case')



In Figure 49, a variation to the Base Case is considered where a single one-off intervention is given but which may not apply for the lifetime of the patient – it is possible to revert to an unenhanced state and no longer be eligible for enhancement. In this scenario there is simply no reason to approve the enhancement (it is expensive, not cost-effective and causes inequality). This is the corollary of the scenario described in Figure 48, where the decision is so obvious that applying existing HTA methods results in a sensible conclusion regardless of whether those methods are entirely fit for purpose. In general, from this point on, we consider only more complex scenarios.

C.2.3. 'Partial eligibility' case

Figure 50 – Base Case Variation 3 ('Partial eligibility case')

Results

Base case

Decision	APPROVE
ICER	£25,418

Societal case

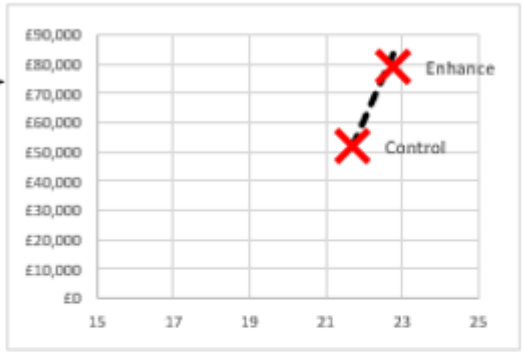
Decision	APPROVE
ICER	£25,418

Tapering case

Decision	REJECT
ICER	£35,710

Capping case

Decision	REJECT
ICER	£60,006



Equality outcomes	
NHS budget impact	52.23%
Probability harm	0.00%
Vertical equity index	0.60
H'zontal equity index	0.70
Rawlsian equity index	1.08

Finally, in Figure 50 a variation is described where only 10% of patients are eligible for enhancement (the remaining 90% of patients simply do not respond to the pharmaceutical treatment and do not try again, for example). This scenario is included to demonstrate that enhancement can have a significant impact on equity despite the fact the Base Case does not – health inequality is greatly increased across all dimensions, meaning that even though the cost-effectiveness case between the Base Case and the Figure 50 variation is essentially identical, the social value judgement could easily be that it is not worth spending such a significant sum of money to merely increase health inequality. This judgement cannot be made in a vacuum (for example, almost everyone would agree that it is highly relevant *which* 10% of the population can be enhanced), but is good support for the claim that equity arguments are important to consider when modelling enhancement outcomes.

C.3. Variations to ‘benefit society’ cases

This subsection considers variations to the ‘Benefit society’ main results in Section 4.6, as part of the more general strategy of sensitivity analysis discussed in Appendix C.1.2.

C.3.1. The problem is not strictly enhancement-specific

One immediate finding from the HTA model is that the issue of significant externalities could theoretically occur at any point in the HTA process (that is, it is not specific to enhancements) For

example, Figure 51 demonstrates that the effect in Figure 19 – Base Case Initialisation parameters (unchanged in subsequent outputs unless otherwise noted)

Initialisation	
Technology scenario	Standard
Posology scenario	Branded pharmaceutical
Eligible population	68,000,000
Notes	*No special notes*

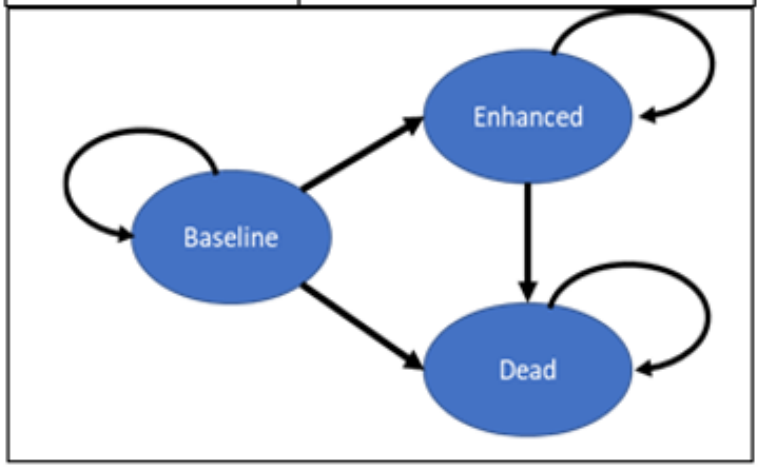


Figure 20 where the NHS follows its own rules and bankrupts itself can occur in an entirely non-enhancement context by the addition of a significant externality benefit to a conventional technology (if the HTA body adopts that perspective). It is probably fair to say that enhancements make this sort of impact more likely, since the externality parameters required in order to make the scenario in Figure 51 work are rather extreme and unlikely to occur in a conventional context. Nevertheless, it is surprising that this issue is so under-theorised in the literature

Figure 51 – Model output for NHS Subverting Externality case

Results

Base case

Decision	REJECT
ICER	£36,373

Societal case

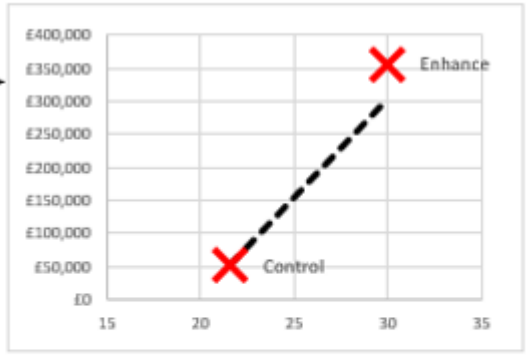
Decision	APPROVE
ICER	£7,436

Tapering case

Decision	REJECT
ICER	£51,183

Capping case

Decision	REJECT
ICER	£86,341



Equality outcomes	
NHS budget impact	5057.31%
Probability harm	0.00%
Vertical equity index	0.71
H'zontal equity index	0.99
Rawlsian equity index	1.37

C.3.2. Liberty implications of societal perspective

Not discussed by these authors, although important to understanding the implications of these approaches on HTA outcomes is that that some treatments which currently rest in Cluster 6 (which are harmful and cost-ineffective) would be brought into the South-West Quadrant of Cluster 2 or 3 by following either of these enhancement specific HTA strategies. Arguably there is ethical repugnance in this regardless of which strategy is followed; in the case of Buchanan (2008)'s original suggestion, individuals would be directly paid for undergoing harmful but economically productive medical procedures, which could lead to similar issues with inequality as paying people to undergo risky medical procedures in order to test drugs (Dickert & Grady, 1999) – which is to say the poor bare the risk while society in general receives the returns. In the case of Buchanan (2008) suggestion applied to the NHS, the result is a magnified version of the discussions about SW quadrant (Dowie, 2004) – in other words the government would be paying the NHS to harm citizens in exchange for making those citizens more productive, but the NHS could reinvest this money to help other citizens meaning in principle this approach could be ethically appropriate.

C.4. Towards a specification of the Economic Disincentives Model

C.4.1. Overview of the EDM

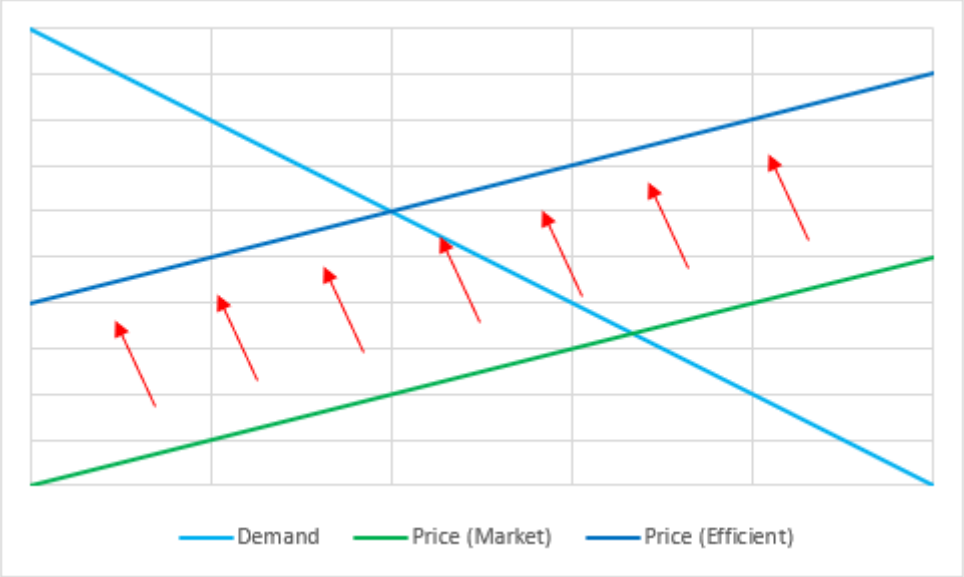
The economic disincentives model (EDM) is the most well-specified health economic theory of human enhancement in the literature. It is described across four papers (Dubljevic, 2012b; Dubljević, 2013a, 2013b, 2015) and broadly seeks to regulate enhancements by mandating that people take a test (paid out of their own pocket) before accessing them and take out an insurance policy against the medical costs of an enhancement-induced side-effect. The details of the EDM vary slightly across the four papers in which it is described, and these variations are discussed below.

The economic logic of the Economic Disincentives Model (EDM) is to effectively decrease demand to arbitrary levels by making the acquisition of enhancement technologies unpleasant in some way – to add an economic disincentive to counterbalance the presumably large incentive of enhancing yourself (Dubljevic, 2012b; Dubljević, 2013a, 2015). This can be modelled as a form of Pigouvian tax on enhancement technologies, where the 'tax' contains an inconvenience and financial component. The importance of the 'inconvenience' component is emphasised in Dubljević (2013a), who argues that a simple Pigouvian tax analogous to the tax on cigarettes could create an irresistible source of income for governments who would then be heedless of the risks of new enhancement technologies.

Figure 52, below, represents a model of how the EDM might alter the demand for enhancement. Under a free market the quantity of enhancement demanded is too high to be socially optimal, and therefore the government introduces a tax on the purchase of enhancement. This lowers demand to a level deemed socially optimal. Note the conceptual similarities between Figure 52 and Figure 14 – in fact both models aim at altering market behaviour through the imposition of an externally-imposed price rise or fall (depending on whether they think too many or too few enhancements will be purchased in the open market). There is a slight difference between the two models, however, which is that the Buchanan approach illustrated in Figure 14 imagines that enhancements are subsidised financially, whereas the EDM approach in Figure 52 imagines that that enhancements are disincentivised through a mix of financial burden and inconvenient testing and licensing. Therefore, while the financial component of the EDM approach can be used to compensate society for the

externality effects of enhancement, the inconvenient licensing is pure deadweight loss with no analogue in the 'Benefit society' models. Note that Dubljević might disagree with this characterisation, arguing that the education and test is socially efficient if it helps people understand the risks of a particular enhancement –e.g. he compares the efficiency and legitimacy of EDM to vehicle driving licencing procedures in Dubljevic (2012b).

Figure 52 – Conceptual representation of a Pigouvian tax being used to lower demand for enhancement by increasing price to match the efficient supply level, analogous to the EDM approach. Red arrows represent the combined inconvenience and financial component of the EDM raising prices.



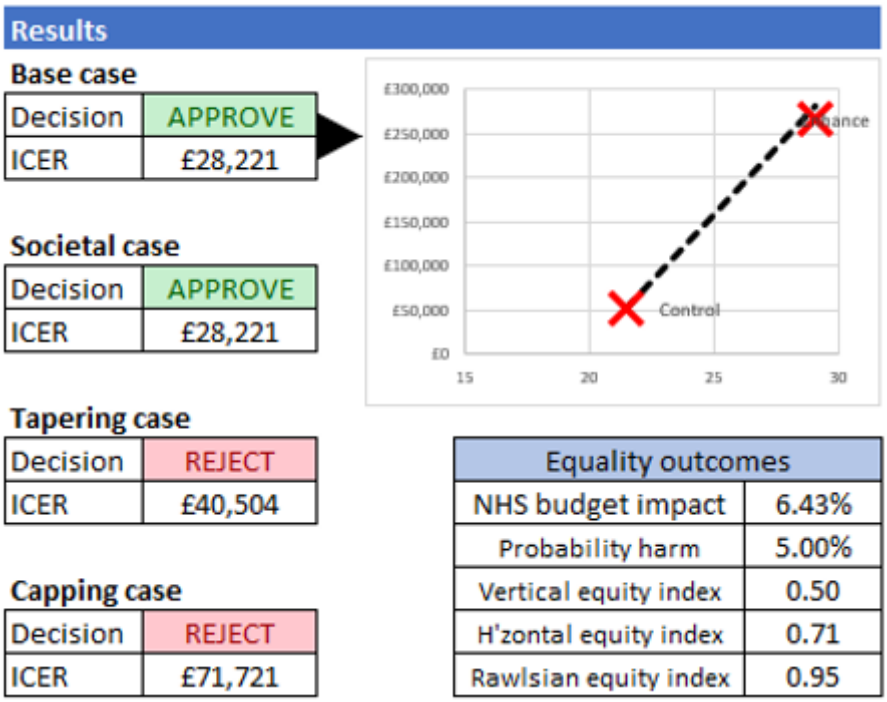
C.4.2. Implementation difficulties

Unlike the other approaches, which call for different methods of distributing resources within the existing NHS framework, the EDM calls for a radical and wholesale change to the setup of the NHS, where therapies which would normally be regulated by a body like NICE are instead effectively available 'over the counter' for anyone capable of passing the test Dubljevic envisages. Dubljevic (2012b) apparently makes some concessions to this point, discussing how some technologies (such as tDCS) would not be suitable for the EDM. Nevertheless, it is a reasonable principle to suggest that the more radical the reform – and the EDM is extremely radical – the stronger the justification would have to be to undertake it, or else protecting the NHS from one risk merely devolves into another.

C.4.3. Equality impact

As discussed in Chapter 3, a risk of the EDM is that it appears to create equalities issues however it is specified. Figure 53 demonstrates that it is possible to create an enhancement with a low risk of a high-cost impact, which would neseccitate a relatively expensive insurance policy to indemnify the NHS against the harm. But as this insurance policy would be budget neutral according to Dubljevic, this means the insurer must charge around £30,000 (i.e. the average UK annual income), making the enhancement out of reach to all but the richest. We might also consider that a technology which is indicidually rational to purchase (even with insurance) but which nevertheless maims half of those who take it is not the sort of technology which thje NHS should allow people to purchase just on the basis of a cognitive test (if at all).

Figure 53 – Model output for impossible-to-insure case



C.4.4. Efficiency impact

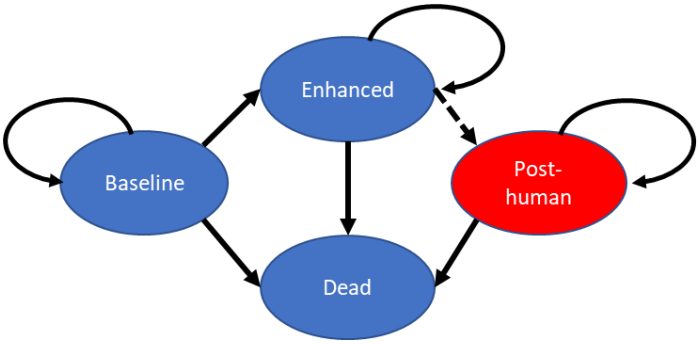
However, as a tradeoff to this, the EDM interacts very well with some traditionally cost-ineffective technologies, including enhancement technologies that might be cost-ineffective. As the EDM internalises some of the cost of the NHS purchasing these technologices, it can help identify those whose private valuations of these technologies is higher than average and therefore improve the economic efficiency of valuation of technologies of this kind. In the case of cost-effective

technologies the same argument applies in reverse, although note that here deadweight loss is created when the 'tax' of the EDM prevents people from getting enhancements they otherwise would have benefitted from. It is possible Dubljevic had in mind that the EDM should only apply to these technologies, where arguably the EDM does provide more consistent decision making (albeit with severe equality tradeoffs). Nevertheless, as argued in the conclusion – since we do not yet know that enhancements will be limited to the three more 'straightforward' types, we cannot implement the EDM without strict safeguards preventing tragedy if technologies in the three less 'straightforward' clusters are invented.

C.4.5. Rational addiction to enhancments

It is possible to construct situations where individual will enhance even if the population as a whole is strictly *worse* off than they would have been otherwise. In a simple fashion, there may be a negative externality associated with enhancement, but it is likely Dubljevic would council increasing the 'tax' to cover the costs of these. However, in a more complex model, such as that depicted in Figure 54, the enhancement might be such that it alters the ends of the person being enhanced – for example making them more likely to want to enhance again in the future.

Figure 54 – Example model input for a 'Rational Addition' model



For example, a violent man might take a mood stabiliser to make him less violent. Upon becoming more filled with love and compassion for his fellows, he might reflect with horror on the fact that he eats meat and the suffering that this causes animals (something he never worried about before), and take further mood stabilisers to suppress the desire to do this. Upon taking these drugs, he might worry about the insects killed by his footfalls, and so on. Each step in the process makes the man more unhappy, but the force of the argument compels him to keep going. This has echoes of Becker's

Rational Addiction Model, where becoming 'addicted' to enhancement could be part of a consistent plan to maximise utility over the long term (Becker & Murphy, 1988).

C.4.6. Conclusions

If the EDM was used only for enhancements with a low cost, a minor impact on quality of life and no other unusual characteristics then it is plausible it offers a superior decision-making algorithm to conventional health technology appraisal, since it internalises costs and benefits and therefore prevents many of the unwanted mechanisms described above from occurring (such as adverse selection and moral hazard). It does not appear to offer significant improvements over the conventional HTA process when the stakes are higher, to the extent that depending on the enhancement technology's characteristics it can underperform the HTA process. In addition, it is not clear if the public would regard paying for (some) enhancement healthcare as an unacceptable outcome given the strong belief in many countries that healthcare should be free at the point of use, or at least not priced such that it disincentivised seeking care.

Overall, it seems that the EDM contains much valuable economic insight, but it is difficult to create a genuinely well-specified version of the EDM which does not have edge cases that are hard to justify. Consequently, the most sensible treatment of the EDM in the thesis is as the inverse of a subsidy, where much of what makes the EDM subtle and interesting is removed to focus entirely on the function as a Pigouvian tax.

C.5. Variations to 'inequality targeting' cases

C.5.1. Not enhancement specific

Note that as with the externality issue, this is not specifically a problem with enhancements; enhancements only magnify a value judgement which must be made anyway in conventional technology appraisal. The specific issue caused by enhancement is that the potential level of *ex post* inequality is boundless; whereas inequality in conventional treatment is formally bounded by the fact that no group can ever have better than QoL > 1, inequality is not so bounded in the context of enhancements.

C.5.2. Compensation

Ray (2016) suggests that those who are *ex ante* disadvantaged receive enhancement to compensate them for this disadvantage and render *ex post* inequality as close to zero as possible – addressing vertical and horizontal inequality. Figure 55 depicts a scenario where the 'disadvantaged' archetype are enhanced and the 'advantaged' archetype are not which actually **increases** inequality (since the enhancement is much better than being *ex ante* advantaged) but this is not a serious objection to Ray – Figure 56 depicts a scenario where a linear combination approach to ensure *ex post* inequality between the two groups is exactly equal to zero (note that this is inequality *between the groups* (horizontal inequality) – there is still some vertical inequality which persists due to random variation in outcomes within the group).

Figure 55 – Equity Variation 2: Inequality targeting (but 'overshooting')

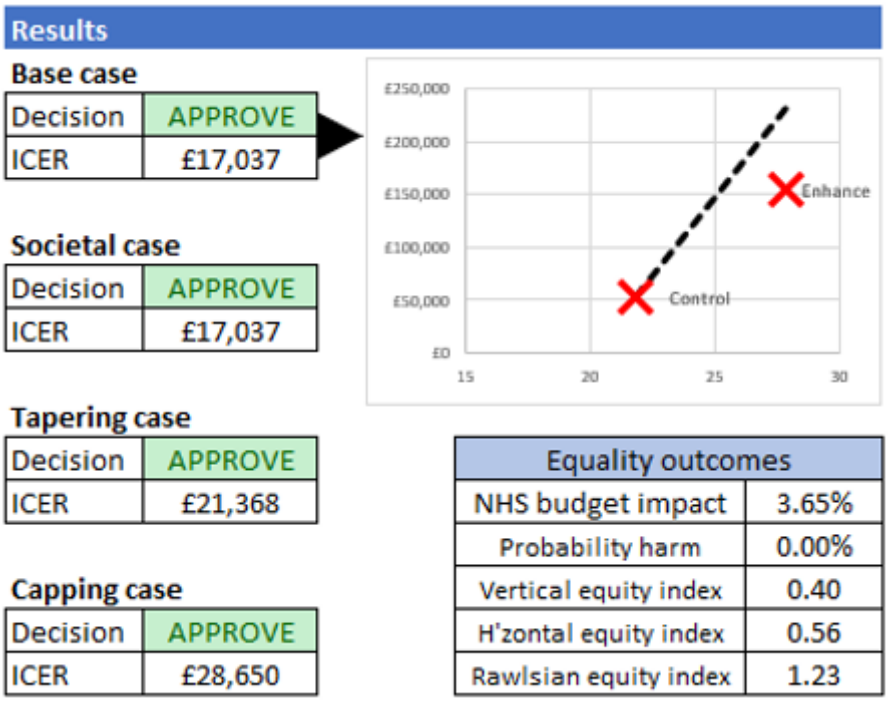
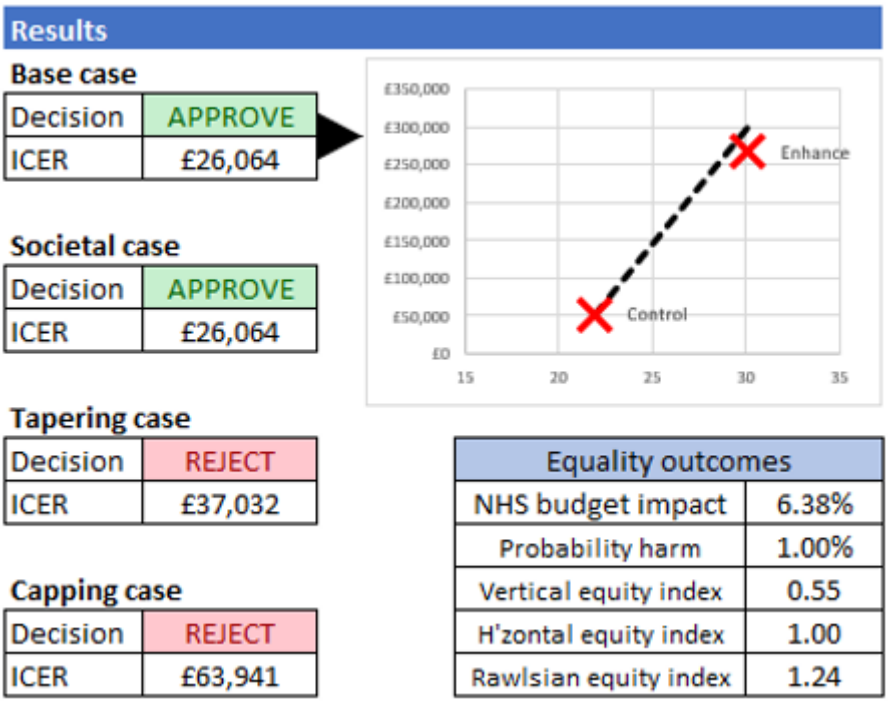


Figure 56 – Equity Variation 3: Inequality targeting (with perfect ex post horizontal inequality)



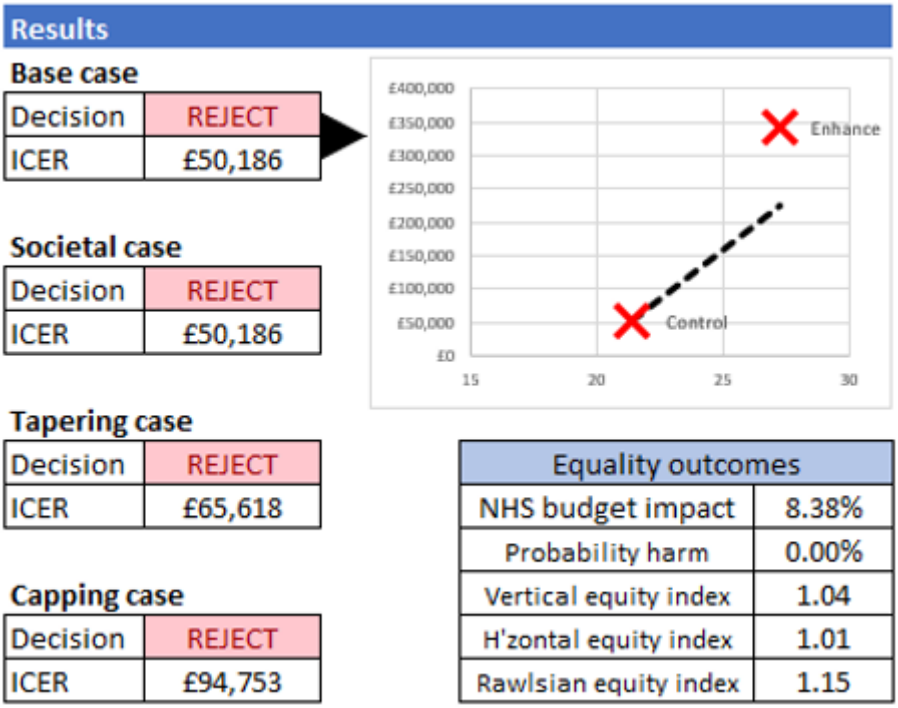
Note also that the figure described as 'horizontal equity' in Figure 55 and Figure 56 is actually an index comparing the ex post to ex ante situation. Therefore, a score of 1 indicates that the ex post and ex ante situation are comparable (ie embedding existing inequality). For the sake of demonstration, this was selected instead of true horizontal equity, since that state has no natural interpretation in the results diagram

With minor changes, this technique can also be used to target a given level of vertical equality or to ensure that *ex post* equality is achieved between more than two groups. The downside of Ray's approach is that the more stringent the constraints placed on equality outcomes the less able society is to achieve the most welfare enhancing outcomes (which is not a new finding, being essentially a restatement of the well-described equity-efficiency tradeoff (Wagstaff, 1991)). This is demonstrated in Figure 55 and Figure 56 – the ICER for Figure 55 (which has only a very minor equality constraint) is a comfortable approve, whereas the ICER for Figure 56 (which has a more restrictive equality constraint) is only a marginal approve. It is not difficult to add further constraints such that there is no achievable outcome which both satisfies these constraints and is approvable under conventional HTA methods. Furthermore, it can be incompatible to target both strong horizontal / vertical equality and strong Rawlsian equality using these techniques, for example if preserving horizontal equity requires harming the disadvantaged a little in order to harm the advantaged a lot. This too is an extremely well discussed problem in the philosophy of utilitarianism (Parfit, 1984)

C.5.3. Reparations

Lavazza (2019) considers the same problem from a different angle, arguing that those who cannot get enhanced (or do not wish to enhance) are victims of an unchosen disadvantage and therefore should be financially compensated. Figure 57 depicts such a setup where the unenhanced incur an externality cost to represent transfers from the government to those who cannot or do not wish to enhance.

Figure 57 – Model output showing a technology which would be approvable except for compensating the unenhanceable to achieve near-zero health inequity



In contrast to Ray, Lavazza's solution is both an efficiency frontier and has zero *ex post* vertical inequality. The downside of Lavazza's solution is that it is significantly expensive – Figure 57 depicts a situation where an enhancement would benefit society and would be accepted under conventional HTA criteria, but is rejected under the Lavazza criteria since the compensation element edges the ICER over £30,000 / QALY. It should also be added that Lavazza's solution is only definitely an efficiency frontier in the toy example of Figure 57 – in real life we might be concerned about adverse selection (individuals choosing which archetype to be based on their personal conception of the good – see for example Akerlof (1978)) where individuals who value money more than enhancement but value enhancement more than non-enhancement might choose to remain unenhanced in order to take the money, depriving the world of the various benefits of their enhancement. The model is not well

specified to account for adverse selection (recalling **Table 5**, an agent-based model would be required), however just from economic theory we can see that deadweight loss is to be expected if people who would have benefitted from enhancement instead take the cash payment.

C.6. Variations to network effects case

C.6.1. Network effects

Savulescu et al. (2011) discusses how there may be intangible social benefits of enhancing society. They observe that richer societies have more spare income to devote to helping poorer and weaker members of that society and have more capacity and inclination to create meaningful cultural and social institutions. They note also that many desirable traits are distributed along a curve (for example there are only a very small number of world-class opera singers, a large number of people who can carry a tune reasonably well and only a small number of people who are completely tone deaf). In the view of Savulescu et al. (2011), small changes to the mean of these distributions could produce significantly more outstandingly talented individuals. While Chapter 3 classifies this as a straightforward externality position, actually modelling Savulescu et al. (2011) demonstrates that this is not quite correct, and in fact it is more like a network effect of enhancement.

C.6.2. Enhancing pressure

Lamkin (2011) proposes a similar but more economically nuanced model, where the externality effect of more people being enhanced harms the unenhanced, rather than the enhanced themselves. This means that the finding described in Figure 61 will not hold, since the unenhanced population are harmed by the actions of the enhanced and thus warehouse managers actually do care whether other jobs take mathematics enhancements. Lamkin's specific example should probably be read as a *reductio* on the concept of enhancement itself, but the economic intuition can be drawn out by considering a scenario where remaining unenhanced adds a disutility the more people who choose not to enhance. This is described as the 'Hipster' archetype in the model to signify that nobody wants to be the last person to adopt the new trend and is shown in Figure 58. The extent to which harm is done to the unenhanced is artificially varied to show a marginal 'accept' case in HTA.

Figure 58 – Externality Variation 4: Enhancing Pressure

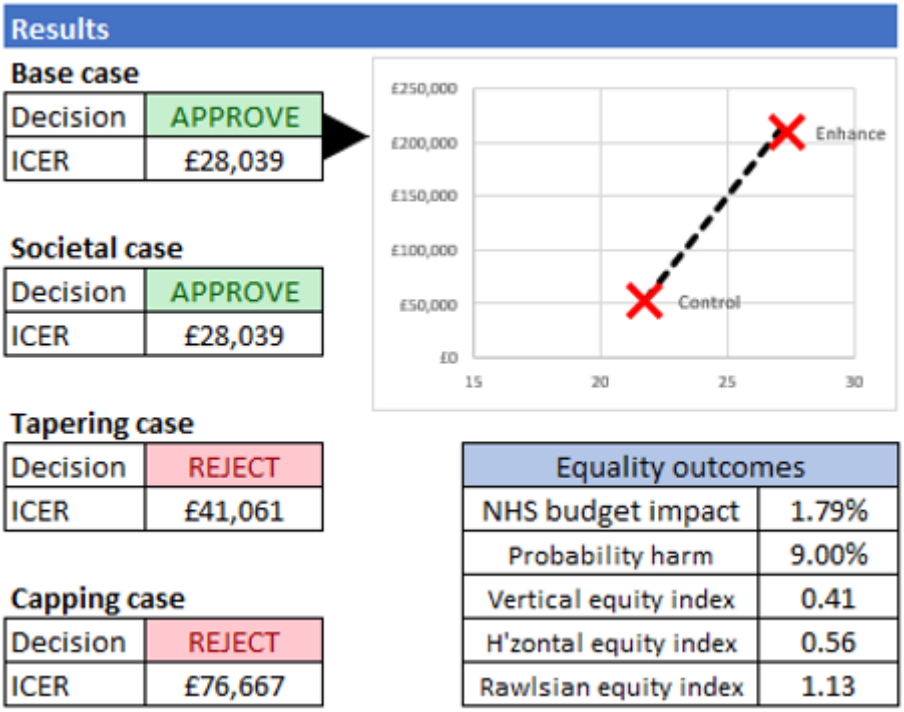
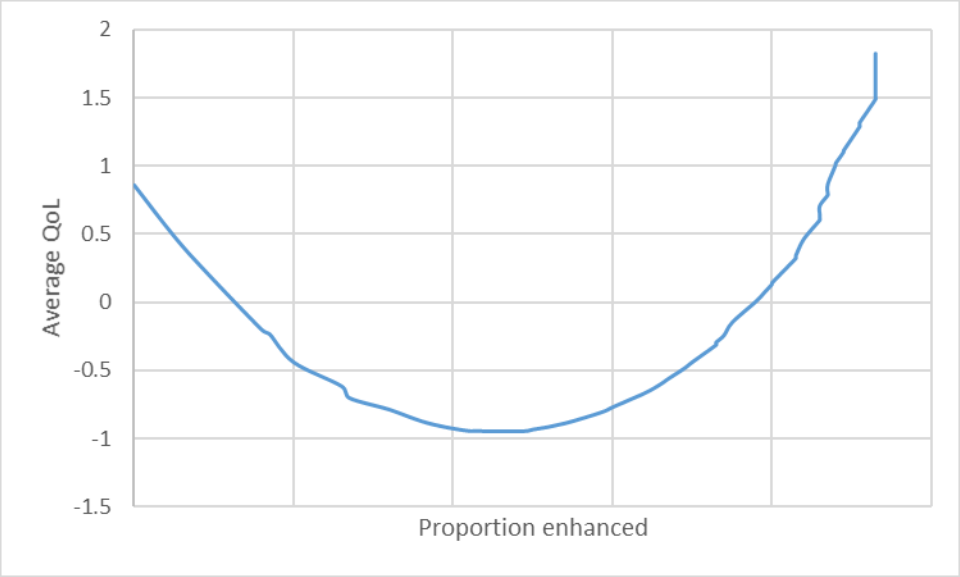


Figure 59 demonstrates a novel and important finding which Lamkin (2011) does not consider – in cases where remaining unenhanced creates a disutility in proportion to the number of enhanced individuals, there are effectively two stable equilibria. One is on the far left of the graph where nobody enhances (and hence there are no enhanced individuals to create negative externalities), and one is on the far right where almost everybody enhances (and hence there are no unenhanced individuals to receive negative externalities). This suggests that – like with Figure 61 – government intervention can prevent the negative outcomes associated with the externality harm.

Figure 59 – Externality Variation 4 analysis, showing proportion enhanced vs average QoL

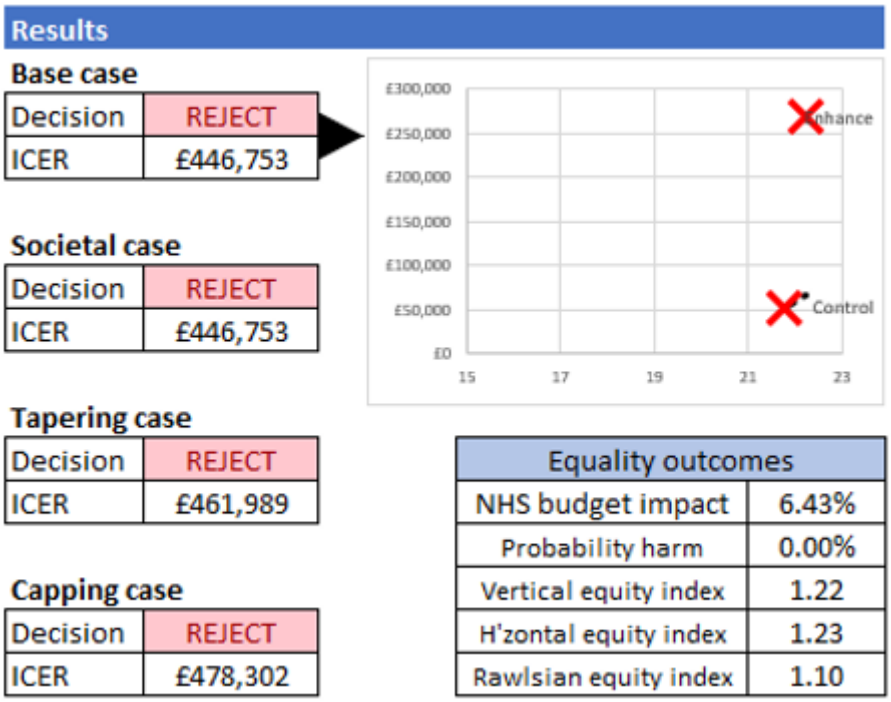


C.6.1. Positional externalities

This notwithstanding, there do appear to be externality issues which are specific to enhancements. For example, Goodman (2010) describes the risk that many enhancements are 'positional', in the sense that the relative level of some characteristic matters more than its absolute value. For example, we might assume 'attractiveness' is an important characteristic to people looking for a sexual partner. If any individual was made more attractive (for example via cosmetic surgery) then they will have a relative advantage over their unenhanced peers. However, if everyone was made more attractive by the same amount then nobody has a relative advantage and the enhancement was pointless. Figure 60 demonstrates this by assuming that any health benefit accruing to an enhanced individual creates a proportional dis-benefit for unenhanced individuals. This is described as the 'Red Queen' archetype in the model, since all actors in the model have to enhance further and further to remain in the same (relative) place.

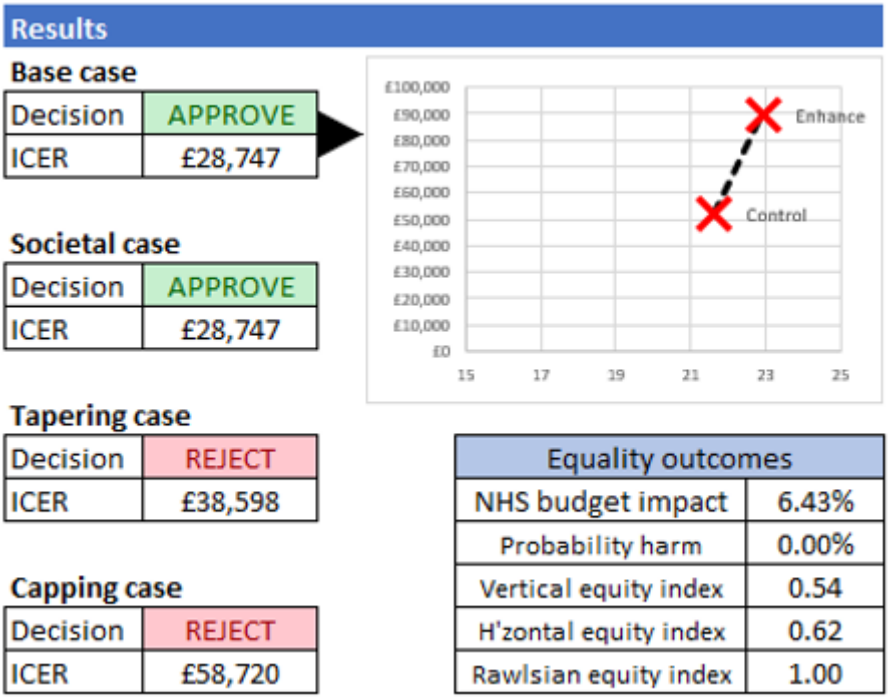
The result is that nearly 7% of the NHS' budget would be spent on a mere handful of QALYs, since QALY gain only really occurs in situations when others unexpectedly lose their enhancement. Although this Figure has some interesting modelling characteristics, it does not appear to imply a significantly different interpretation than the basic externality model described in Figure 51, even though it is enhancement-specific (although note that in this case the externality is internalised as a function of the model, so results are different from Figure 51).

Figure 60 – Externality Variation 2: Positional externality case (full population)



One novel finding of the model is that technologies of this sort do not always result in a 'Red Queen' situation as described in Goodman (2010) where it is impossible for anyone to benefit from the technology. Figure 61 demonstrates that if the technology is restricted to only allow around 15% of the population to enhance, the overall welfare of the population is enhanced at a price considered to be cost-effective (even though this approach results in radically unequal outcomes). This could occur if only a certain segment of the population cared about what the positional enhancement offered (for example Rajczi (2008) describes how warehouse managers have less need for mathematical enhancements than certain other jobs, and so would not care about the positional advantage additional mathematical ability granted them), but given the role of HTA in restricting access to technologies as part of a welfare maximisation strategy it could also be achieved through the government literally 'picking winners' as part of this welfare maximisation strategy.

Figure 61 – Externality Variation 3: Positional externality case (partial population)



For example, consider a simple model based on Lin and Allhoff (2008) and depicted in Figure 62. Society consists of two archetypes – 'enhanceable' and 'unenhanceable'. Both start with the same health-related quality of life and life expectancy, but following enhancement the 'enhanceable' group have significantly better outcomes, leading to significant *ex post* horizontal and vertical inequality (though note that one interesting finding of the Clustering Model is that often Rawlsian inequality anticorrelates with horizontal and vertical inequality in an enhancement context, as in this case). Lin and Allhoff (2008) are especially concerned that the differentiating feature between 'enhanceable' and 'unenhanceable' might be financial security (as they are writing in a US context) but this problem persists even if the differentiating factor is – for example – a specific genetic mutation and so likely to be a problem in the UK.

Figure 62 – Equity Variation 1: Simple equity case

Results

Base case

Decision	APPROVE
ICER	£25,184

Societal case

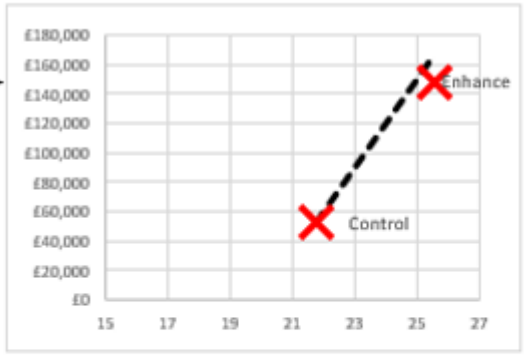
Decision	APPROVE
ICER	£25,184

Tapering case

Decision	REJECT
ICER	£35,236

Capping case

Decision	REJECT
ICER	£58,643



Equality outcomes	
NHS budget impact	6.43%
Probability harm	0.00%
Vertical equity index	0.29
H'zontal equity index	0.38
Rawlsian equity index	1.09

Appendix D. Additional Material on Chapter 5

D.1. Further information on PSA

D.1.1. PSA Code

```
Sub RunPSA2()

Application.Calculation = xlCalculationManual
NumberOutputVariables = 120

Dim PSAOutput()
ReDim PSAOutput(NumberOutputVariables)
NumberRuns = InputBox("How many PSA runs?")

'Sets the model to a know state - specifically, calls the base case and
then activates a switch that samples probabilistically from this case. Code
not shown because it is just loading specific cells from the main model
into memory.
Sheets("PSA Results").Range("d9:dt9999").ClearContents
Call ResetDefaults
Call SwitchRandom

For j = 1 To NumberRuns

    Sheets("PSA Results").Range("E8:DU8").Copy
    Sheets("PSA Results").Range("E10").Offset(j).PasteSpecial
Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
Calculate

Next j
```

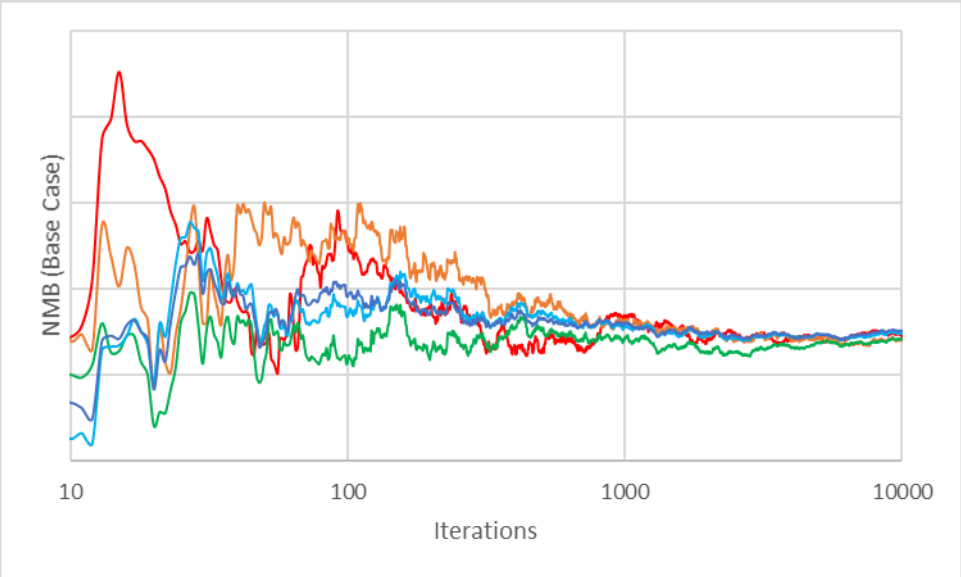
```
'Returns the model to its previous state. Again, code not shown as it is
just unloading data from memory to specific cells.
Call ResetStored
Application.Calculation = xlCalculationAutomatic

End Sub
```

D.1.2. PSA Convergence

Figure 63 shows the convergence of five runs of the PSA performed over 10,000 iterations each. Since performing PSA at a higher number of iterations means that both the PSA itself takes longer and subsequent kNN clustering takes much longer, 1,000 iterations was selected as the best balance between speed and empirical adequacy – moving from 100 to 1000 iterations decreases the sum of squared residuals by 98%, but moving from 1000 to 10,000 iterations reduces it by only 80%.

Figure 63 – PSA Convergence



D.1.3. PSA Output

Table 24 gives an example of typical PSA output by showing the complete output from the first five elements of a PSA run.

Table 24 – Example PSA outputs

	Example 1	Example 2	Example 3	Example 4	Example 5
Error?	0.00	0.00	0.00	0.00	0.00
1.1 - Approvable Base ICER?	1.00	1.00	0.00	1.00	1.00
1.2 - Approvable Societal ICER?	1.00	1.00	0.00	1.00	1.00
1.3 - Approvable Capped ICER?	0.00	1.00	0.00	1.00	1.00
1.4 - Approvable Tapered ICER?	0.00	0.00	0.00	1.00	1.00
1.1 (Alt) - NMB (Base)	101727	359514	-39969	69402	0

1.2 (Alt) - NMB (societal)	101727	359514	-39969	69402	0
1.3 (Alt) - NMB (QoL <1 Only)	-144280	-59635	-39969	59164	0
1.4 (Alt) - NMB (QoL taper)	-43417	267301	-39969	67867	0
2.1 - Total Spend (first year, proportion budget)	0.00	0.43	0.00	0.01	0.01
3.1 - Meaningful impact?	0.00	1.00	0.00	0.00	0.00
3.2 - Probability harm	0.36	0.00	0.88	0.34	0.00
3.3 - Absolute harm	-2.01	0.00	-2.27	-1.53	0.00
4,1 - Rawls index	1.46	1.36	0.75	1.06	1.00
4.2 - SII Index	1.67	0.72	0.94	0.95	1.00
4.3 - AUCCC Index	1.78	1.06	0.92	0.96	1.00
UK Population	68000000	68000000	68000000	68000000.	68000000
NHS Budget (£billion)	140.00	140.00	140.00	140.00	140.00
Population eligible	0.01	0.01	0.01	0.01	0.02
Starting age	46.00	47.00	33.00	27.00	20.00
Cost age dep?	No	No	No	No	No
QALY age dep?	Yes	Yes	Yes	Yes	Yes
QoL Taper	0.41	0.78	0.70	0.85	0.77
Discount unenhanced costs	0.00	0.00	0.00	0.02	0.02
Discount unenhanced QALYs	0.00	0.00	0.00	0.06	0.00
Discount enhanced costs	0.02	0.02	0.04	0.02	0.00
Discount enhanced QALYs	0.04	0.00	0.06	0.06	0.06
Unenhanced Base NHS Costs	1207	276	2435	3032	1613
Unenhanced Base Societal Costs	0.00	0.00	0.00	0.00	0.00
Unenhanced QALYs	0.73	1.11	0.80	1.03	0.49
Unenhanced Mortality HR	1.00	1.00	1.00	1.00	1.00
Enhanced Base NHS Costs	0.15	0.00	0.00	0.00	0.00
Enhanced Base Societal Costs	0.00	0.00	0.00	0.00	0.00
Enhanced QALYs	1.39	1.41	0.92	0.67	0.77
Enhanced Mortality HR	0.80	0.80	0.80	0.80	0.80
Diseased Base NHS Costs	4153	4087	4007	6776	5036
Diseased Base Societal Costs	0.00	0.00	0.00	0.00	0.00
Diseased QALYs	0.73	0.72	0.34	0.03	0.36
Diseased Mortality HR	1.20	1.20	1.20	1.20	1.20
Enhanced Disease Base NHS Costs	4822	4236	3899	2423	3192
Enhanced Disease Base Societal Costs	0.00	0.00	0.00	0.00	0.00
Enhanced Disease QALYs	0.66	0.60	0.54	0.79	0.84
Enhanced Disease Mortality HR	1.00	1.00	1.00	1.00	1.00
Posthuman Base NHS Costs	5237	1480	3112	3263	1760
Posthuman Base Societal Costs	0.00	0.00	0.00	0.00	0.00
Posthuman QALYs	0.11	0.09	0.07	0.05	0.09
Posthuman Mortality HR	0.01	0.01	0.01	0.01	0.01
Enhancement posology	Minor surgery	Major surgery	Generic pharmaceutical	Generic pharmaceutical	Branded pharmaceutical
Technology scenario	Post-Human	Standard	Stasis 2	Disease 3	Ban
Slowing value	0.11	0.09	0.08	0.10	0.08
Disease incidence	0.04	0.06	0.05	0.05	0.05
Disease cure prob	0.25	0.28	0.19	0.20	0.18
Enhanced Disease incidence	0.06	0.05	0.05	0.07	0.05
Enhanced Disease cure prob	0.25	0.24	0.27	0.26	0.31
Stasis reversion prob	0.12	0.09	0.12	0.12	0.12
Posthuman transition prob	0.11	0.09	0.11	0.13	0.12
One-off cost, Vaccine	3.41	2.51	3.09	3.03	2.72
One-off cost, Generic pharmaceutical	0.00	0.00	0.00	0.00	0.00
One-off cost, Branded pharmaceutical	0.00	0.00	0.00	0.00	0.00
One-off cost, Minor surgery	160.05	178.33	129.50	127.57	128.55
One-off cost, Major surgery	84763	87288	76522	76115	73720
One-off cost, Ongoing surgery	82020	92766	93386	76509	98573

Recurring cost, Vaccine	0.00	0.00	0.00	0.00	0.00
Recurring cost, Generic pharmaceutical	120	100	96	81	88
Recurring cost, Branded pharmaceutical	10850	10183	8254	9616	7603
Recurring cost, Minor surgery	1.06	0.97	1.36	1.48	1.50
Recurring cost, Major surgery	890	980	1060	1044	1053
Recurring cost, Ongoing surgery	8121	7638	7835	7920	7553
Archetype Number 1 Prob Occur	0.00	0.00	0.00	0.00	0.00
Archetype Number 2 Prob Occur	0.00	0.50	0.50	0.00	1.00
…	…	…	…	…	…
Archetype Number 19 Prob Occur	0.00	0.00	0.00	0.00	0.00
Archetype Number 20 Prob Occur	0.00	0.00	0.00	0.00	0.00
Archetype Number 1 Factor A	N/A	N/A	N/A	N/A	N/A
Archetype Number 2 Factor A	N/A	N/A	N/A	N/A	N/A
…	…	…	…	…	…
Archetype Number 19 Factor B	N/A	N/A	N/A	N/A	N/A
Archetype Number 20 Factor B	N/A	N/A	N/A	N/A	N/A

D.2. Further information on t-SNE

D.2.1. T-SNE code

T-Distributed Stochastic Neighbour Embedding (t-SNE) is used as a visualisation (but not analysis) technique in the chapter. The main reference for the mathematical elements of t-SNE is Van der Maaten and Hinton (2008), with some additional information on parameterisation taken from Van Der Maaten (2009). This technique is preferred to more conventional techniques such as Principal Component Analysis (PCA) since it preserves local data structures, but since visualisation does not affect analysis it is not considered critical which visualisation technique is used.

The technique is unsuitable for Excel and consequently is not included with the main model file. Instead, results of the main model file are exported as a Comma Separated Variable (CSV) file and analysed separately using Python. The Python code is included below. The main reference for how to encode this in a Python framework is Bedre (2021). Two sets of code are presented – a 'simple' codebase which uses a library to perform t-SNE and a 'complex' codebase which undertakes the same operations using only default mathematical function libraries (following the procedures described in Bedre (2021) almost exactly). Since the 'simple' codebase executes significantly faster, this was selected for all subsequent analysis, with the 'complex' codebase used only for validation.

D.2.2. 'Simple' code

```
# import libraries
import pandas as pd
import numpy as np
from sklearn.manifold import TSNE
```

```
from bioinfokit.analys import get_data

# import data from main model
df = pd.read_csv('tSNES.csv')

# perform t-SNE operations
tsne_em = TSNE(n_components=2, perplexity=15.0, n_iter=1000,
verbose=1).fit_transform(df)

# plot t-SNE clusters
from bioinfokit.visuz import cluster
cluster.tsneplot(score=tsne_em)
```

D.2.3. 'Complex' code

```
# import libraries
import numpy as np
import pandas as pd
from sklearn.datasets import load_digits
from scipy.spatial.distance import pdist
from sklearn.manifold.t_sne import _joint_probabilities
from scipy import linalg
from sklearn.metrics import pairwise_distances
from scipy.spatial.distance import squareform
from sklearn.manifold import TSNE
from matplotlib import pyplot as plt
from bioinfokit.analys import get_data
import seaborn as sns
sns.set(rc='figure.figsize':(11.7,8.27)})
palette = sns.color_palette("bright", 10)


# import data from main model
X, y = pd.read_csv('tSNES.csv')

# Set t-SNE parameters. The MACHINE_EPSILON function prevents any division
by zero and could usefully be ported into the 'simple' model to prevent
this kind of error
MACHINE_EPSILON = np.finfo(np.double).eps
n_components = 2
perplexity = 30

# Fit function - start by computing the distance between points, calculate
the joint probability of these pairs and then initialise this embedding
def fit(X):
    n_samples = X.shape[0]
    distances = pairwise_distances(X, metric='euclidean', squared=True)
    P = _joint_probabilities(distances=distances,
desired_perplexity=perplexity, verbose=False)
    X_embedded = 1e-4 * np.random.mtrand._rand.randn(n_samples,
n_components).astype(np.float32)
    degrees_of_freedom = max(n_components - 1, 1)

    return _tsne(P, degrees_of_freedom, n_samples, X_embedded=X_embedded)

# t-SNE function - collapses data into 1D array and then uses gradient
descent to minimise Kullback-Leibler divergence
def _tsne(P, degrees_of_freedom, n_samples, X_embedded):
        params = X_embedded.ravel()
```

```
        obj_func = _kl_divergence

        params = _gradient_descent(obj_func, params, [P,
degrees_of_freedom, n_samples, n_components])

        X_embedded = params.reshape(n_samples, n_components)

        return X_embedded


# This is the most mathematically complex element of the code - it
calculates the probability distribution over the points, then calculates
the Kullback-Leibler divergence, then calculates the gradient of that
function
def _kl_divergence(params, P, degrees_of_freedom, n_samples, n_components):
        X_embedded = params.reshape(n_samples, n_components)

        dist = pdist(X_embedded, "sqeuclidean")
        dist /= degrees_of_freedom
        dist += 1.
        dist **= (degrees_of_freedom + 1.0) / -2.0
        Q = np.maximum(dist / (2.0 * np.sum(dist)), MACHINE_EPSILON)

        kl_divergence = 2.0 * np.dot(P, np.log(np.maximum(P,
MACHINE_EPSILON) / Q))

        grad = np.ndarray((n_samples, n_components), dtype=params.dtype)
        PQd = squareform((P - Q) * dist)
        for i in range(n_samples):
                grad[i] = np.dot(np.ravel(PQd[i], order='K'), X_embedded[i]
- X_embedded)
        grad = grad.ravel()
        c = 2.0 * (degrees_of_freedom + 1.0) / degrees_of_freedom
        grad *= c
        return kl_divergence, grad

# It seems a conventional gradient descent is adequate for this dataset -
therefore more complex machine learning techniques are not needed
def _gradient_descent(obj_func, p0, args, it=0, n_iter=1000,
n_iter_check=1, n_iter_without_progress=300, momentum=0.8,
learning_rate=200.0, min_gain=0.01, min_grad_norm=1e-7):

        p = p0.copy().ravel()
        update = np.zeros_like(p)
        gains = np.ones_like(p)
        error = np.finfo(np.float).max
        best_error = np.finfo(np.float).max
        best_iter = i = it

        for i in range(it, n_iter):
                error, grad = obj_func(p, *args)
                grad_norm = linalg.norm(grad)

                inc = update * grad < 0.0
                dec = np.invert(inc)
                gains[inc] += 0.2
                gains[dec] *= 0.8
                np.clip(gains, min_gain, np.inf, out=gains)
                grad *= gains
                update = momentum * update - learning_rate * grad
                p += update
```

```
                if error < best_error:
                        best_error = error
                        best_iter = i
                elif i - best_iter > n_iter_without_progress:
                        break

                if grad_norm <= min_grad_norm:
                        break
        return p

# plot t-SNE clusters
from bioinfokit.visuz import cluster
cluster.tsneplot(score=tsne_em)
```

D.2.4. Method of visualisation selection

Since t-SNE is stochastic, there is no single visualisation which will always represent a given dataset. As the goal of the technique is to minimise Kullback-Leibler divergence, the code above was run multiple times, and the graph encoding the lowest Kullback-Leibler divergence was selected. For example, in the set of t-SNE outputs below (run on the same inputs) Figure 64 would be preferred to Figure 65 or Figure 66. This does not affect any later analysis, as the t-SNE is for visualisation only.

Figure 64 – t-SNE Example 1; KL divergence after 1000 iterations: 0.488

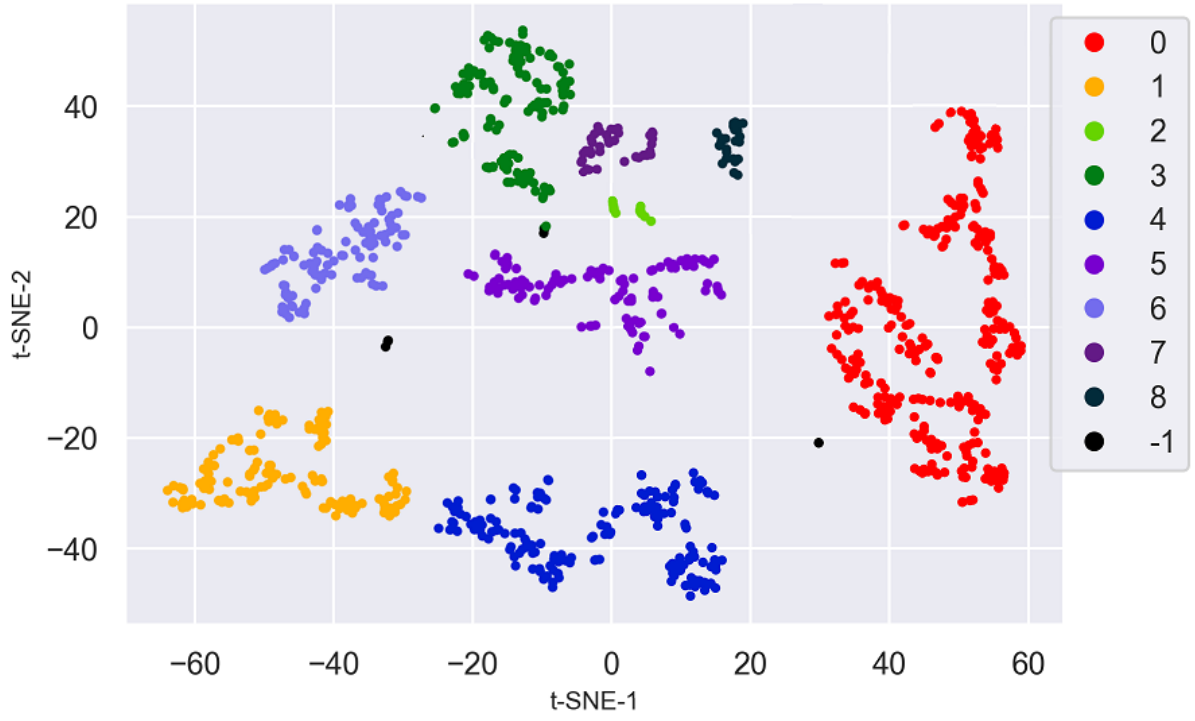


Figure 65 – t-SNE Example 2; KL divergence after 1000 iterations: 0.494

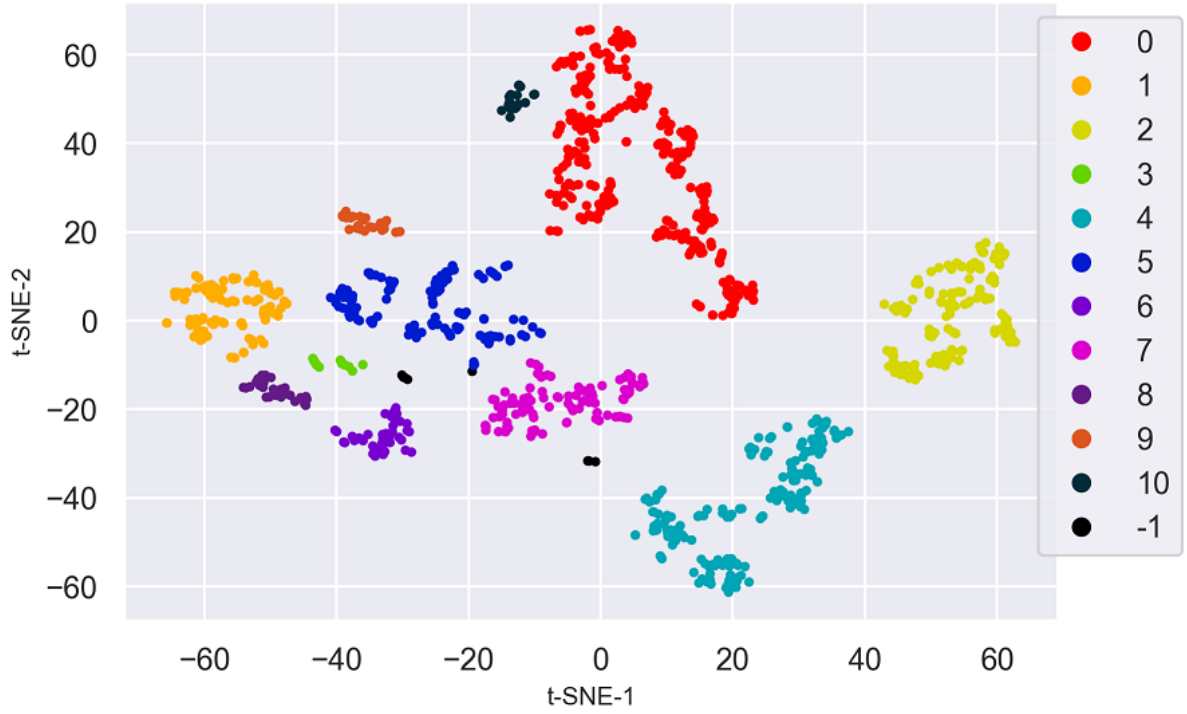
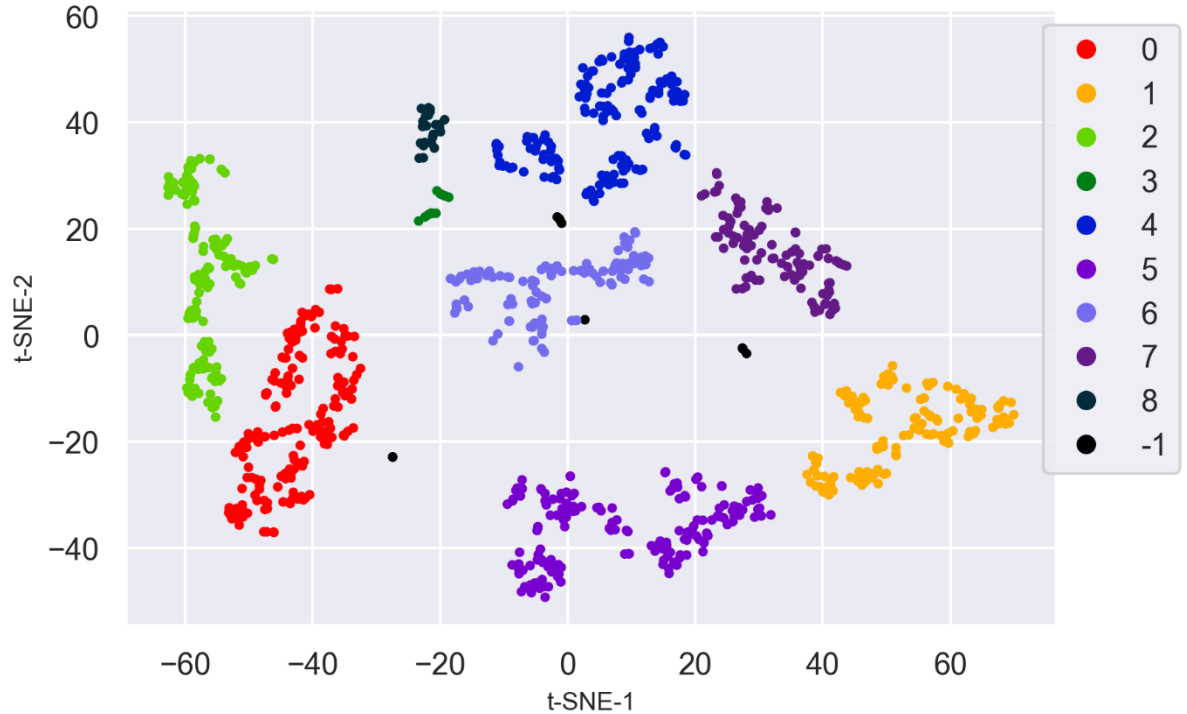


Figure 66 – t-SNE Example 3; KL divergence after 1000 iterations: 0.490



D.3. Further information on k Nearest Neighbour (kNN)

D.3.1. kNN code

Two sets of code are shown below – the 'Single kNN instance' code loops through every relevant centroid and implements a gradient descent function, the 'kNN loop' code calls the 'Single kNN instance' code multiple times. The original intention of the work was to manually resolve the 'Single kNN instance' code until convergence was reached, but this proved impractical at higher numbers of centroids and so the 'kNN loop' code was added towards the end of development to address this issue.

D.3.2. Single kNN instance

```
Sub kNNAnalysis()

MaxTargetScore = 100
NumberVariables = 26
NumberCentroids = Range("B2")

For i = 1 To NumberVariables
    For j = 1 To NumberCentroids

        TargetScore = Range("B3")

        RandValue = 0.05  '* (TargetScore / MaxTargetScore)
        PrevValue = Range("A5").Offset(i, j)

'Since kNN was selected on the basis that outputs would likely be linear,
there seems to be no reason not to pick a linear machine learning technique
- therefore an extremely simple gradient descent is implemented below,
presupposing entirely monotonic input data
'Add the gradient descent function
        Range("A5").Offset(i, j) = Range("A5").Offset(i, j) + RandValue
        If Range("B3") < TargetScore Then
            TargetScore = Range("B3")
            PrevValue = Range("A5").Offset(i, j)
        Else
            Range("A5").Offset(i, j) = PrevValue
        End If

'Subtract the gradient descent function
        Range("A5").Offset(i, j) = Range("A5").Offset(i, j) - RandValue
        If Range("B3") < TargetScore Then
            TargetScore = Range("B3")
            PrevValue = Range("A5").Offset(i, j)
        Else
            Range("A5").Offset(i, j) = PrevValue
        End If

Range("A5").Offset(i, j) = PrevValue

    Next j
Next i

End Sub
```

D.3.3. kNN loop

```
Sub KNNFullAnalysis()

If Range("a19") = 1 Then

Sheets("Processed Data").Range("B2:AA11").Copy

Sheets("Analysis").Range("B6").PasteSpecial Paste:=xlPasteValues,

Operation:=xlNone, SkipBlanks:=False, Transpose:=True

Else

Sheets("Analysis").Range("b6:k31").ClearContents

End If



Range("AP6") = Range("B3")

For Trials = 1 To Range("a18")

      Call kNNAnalysis

      Range("AP6").Offset(Trials) = Range("B3")

Next Trials

End Sub
```

D.4. Validation of centroid selection

Figure 38 gives the justification for selecting six centroids. Three validation tests of this decision are conducted:

In Table 25, centroid weighting for nine clusters is given. Since there is a small improvement in Euclidian distance for nine vs six centroids, this might be a more accurate value to select. The values in green effectively map onto Cluster 1 – they are all highly cost-effective with a significant QALY gain. The values in pink effectively map onto Cluster 6 – they are not cost-effective and are harmful. All other values effectively map onto the six-cluster model directly.

While it is interesting to see a ‘high cost Cluster 1’ and a ‘low cost Cluster 1’, nothing in this distinction would have altered the analysis in the main body of the text. Other than this, the duplicate centroids appear to be substantially overfit and the choice of six centroids is confirmed.

Table 25 – Centroid weighting for nine clusters

Centroid	1	2	3	4	5	6	7	8	9
1.1	0.00	1.00	1.00	0.00	0.00	1.00	1.00	0.00	1.00
1.2	0.00	1.00	1.00	0.00	0.00	1.00	1.00	0.00	1.00
1.3	0.00	1.00	0.44	0.00	0.00	1.00	1.00	0.00	1.00
1.4	0.00	1.00	0.00	0.03	0.00	0.99	1.00	0.00	1.00
2.1	0.03	0.01	0.14	0.55	0.04	0.42	0.55	0.44	0.00
3.1	0.00	0.00	0.00	0.00	0.00	1.00	1.00	0.00	1.00
3.2	0.81	0.01	0.15	0.00	0.17	0.00	0.00	0.41	0.00
3.3	0.20	0.00	0.03	0.00	0.05	0.01	0.00	0.07	0.00
4.1	0.12	0.15	0.17	0.14	0.14	0.22	0.51	0.15	0.23
4.2	0.09	0.05	0.05	0.05	0.06	0.02	0.00	0.07	0.02
4.3	0.15	0.12	0.13	0.12	0.14	0.09	0.03	0.16	0.08

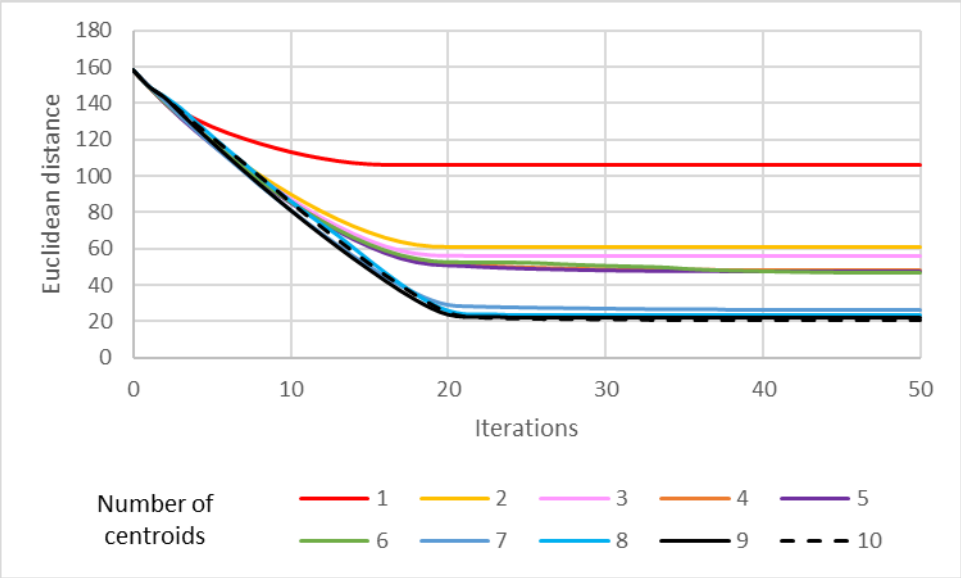
In Table 26, centroid weighting is given using NMB instead of a binary cost-effective or not value. This was not selected for the main analysis because it makes interpretation more difficult, but the results in Table 26 map exactly onto the results of Table 11. The only noticeable difference is that the are some small numerical reweighting with Centroid 3.

Table 26 – Centroid weighting for six clusters, using NMB instead of binary cost-effectiveness

Centroid	1	2	3	4	5	6
1.1 (Alt)	0.24	0.06	0.02	-0.04	-0.09	-0.30
1.2 (Alt)	0.24	0.06	0.02	-0.04	-0.09	-0.30
1.3 (Alt)	0.24	0.02	-0.03	-0.12	-0.21	-0.57
1.4 (Alt)	0.25	0.05	-0.01	-0.07	-0.13	-0.44
2.1	0.11	0.01	0.49	0.02	0.45	0.08
3.1	1.00					
3.2	0.01	0.02	0.00	0.75	0.41	0.95
3.3	0.02	0.01	0.00	0.14	0.07	0.61
4.1	0.22	0.15	0.17	0.12	0.14	0.10
4.2	0.02	0.05	0.04	0.07	0.07	0.21
4.3	0.09	0.12	0.11	0.14	0.15	0.24

Finally, Figure 67 shows an updated Figure 38 using a different training set (the last 10% of iterations). Visual inspection suggests no major differences to Figure 38, validating that this was an appropriate approach.

Figure 67 – Improvement in accuracy by increasing number of centroids using different training set



D.5. Detailed Analysis of Clustering Algorithm Outputs

Figure 68 – Detailed analysis of Cluster 1

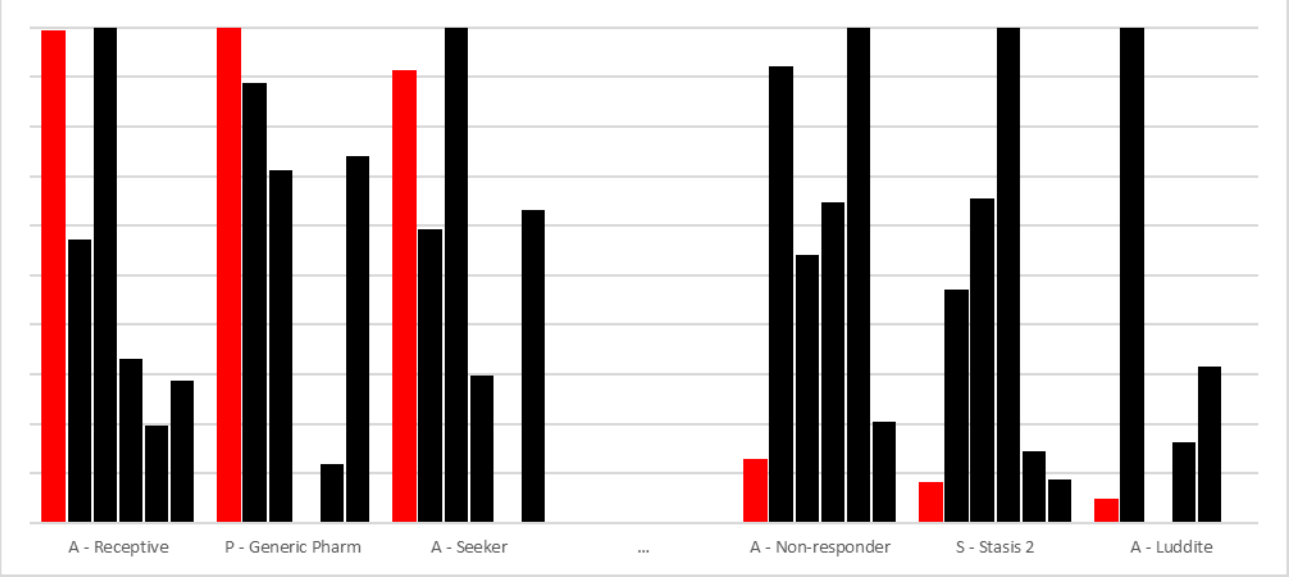


Figure 69 – Detailed analysis of Cluster 2

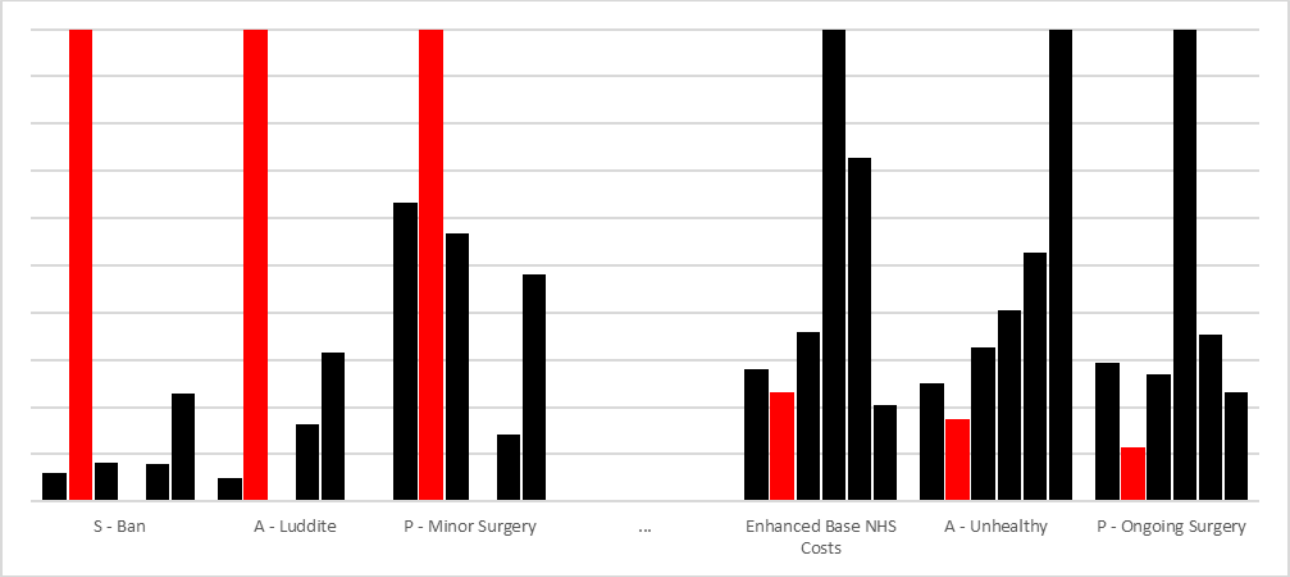


Figure 70 – Detailed analysis of Cluster 3

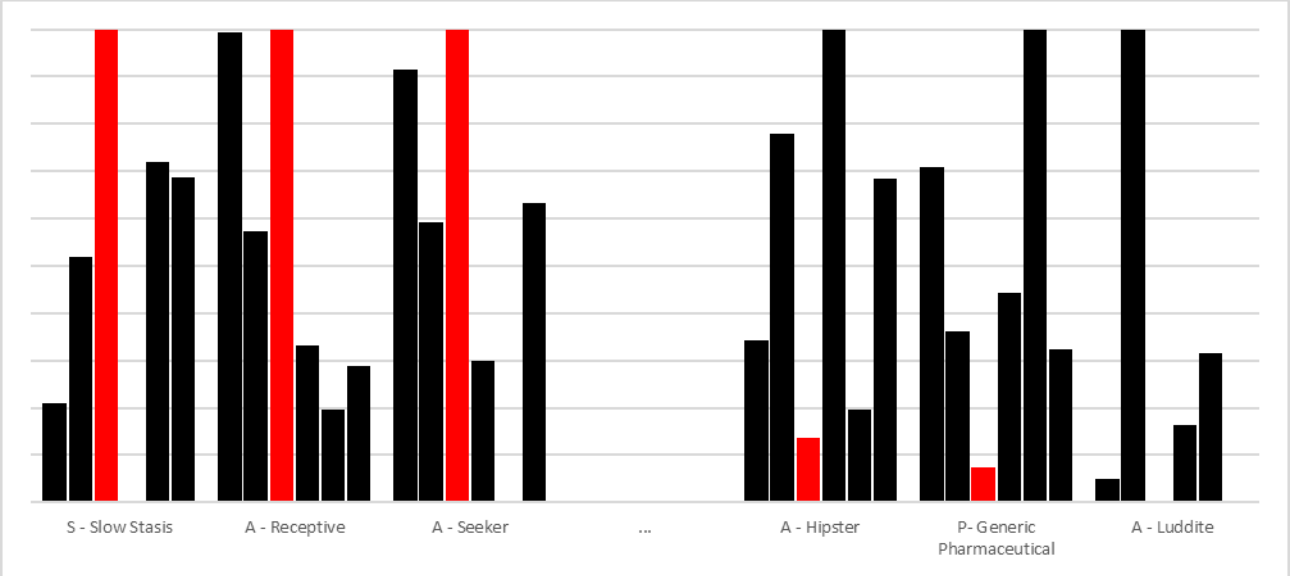


Figure 71 – Detailed analysis of Cluster 4

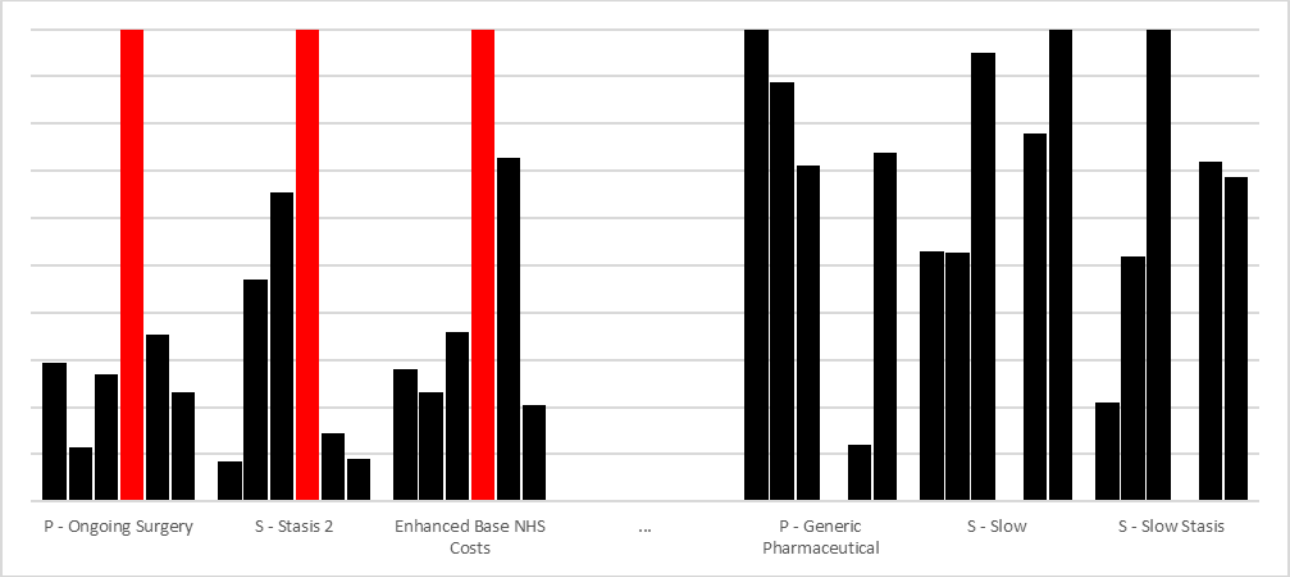


Figure 72 – Detailed analysis of Cluster 5

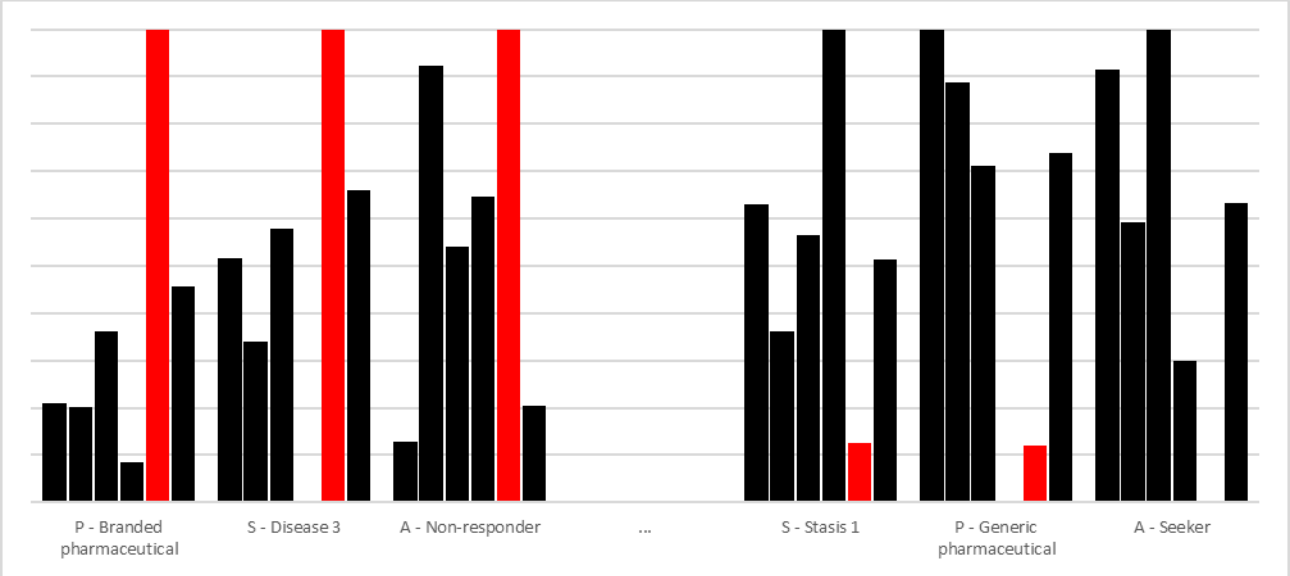
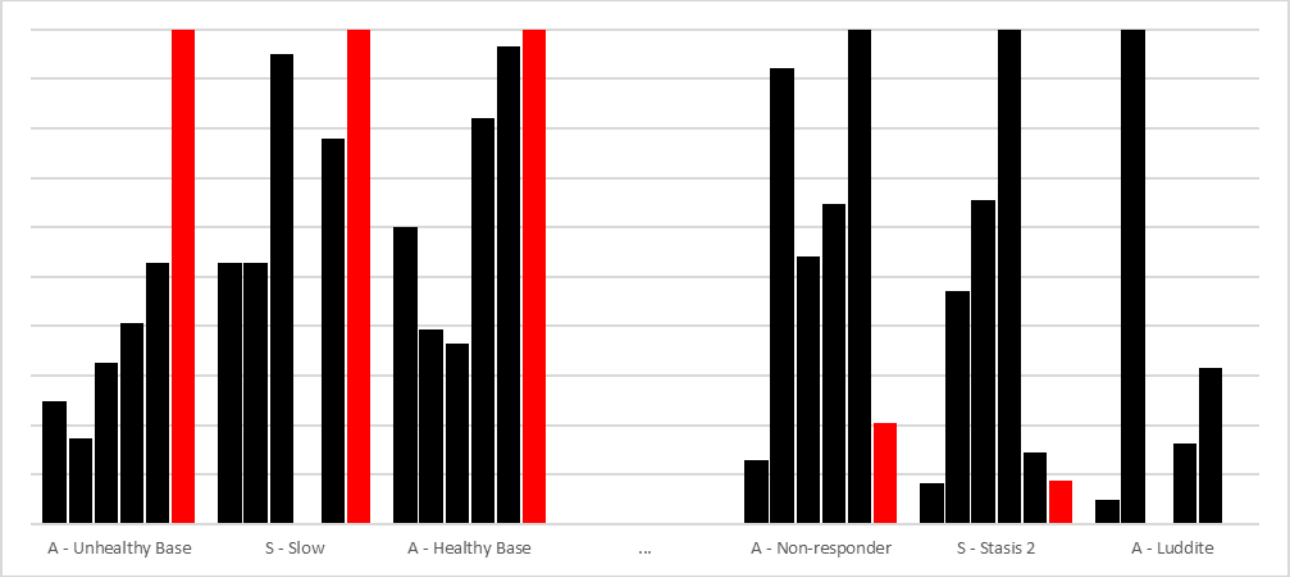


Figure 73 – Detailed analysis of Cluster 6


A - Unhealthy Base
S - Slow
A - Healthy Base
...
A - Non-responder
S - Stasis 2
A - Luddite

Appendix E. Ethics documentation

Faculty of Health and Medicine Research Ethics Committee (FHMREC)

Lancaster University

Application for Ethical Approval for Research

Guidance on completing this form is also available as a word document

Title of Project: "Feeling better than ever?" – Are there any internally consistent responses to the challenge of 'better than perfect' human health enhancement technology in a health technology appraisal context?"

Name of applicant/researcher: Alex Bates

ACP ID number (if applicable)*: **Funding source (if applicable)**

Grant code (if applicable):

***If your project has *not* been costed on ACP, you will also need to complete the Governance Checklist [link].**

Type of study

☒ Involves existing documents/data only, or the evaluation of an existing project with no direct contact with human participants. **Complete sections one, *two* and four of this form**

☐ Includes *direct* involvement by human subjects. **Complete sections one, *three* and four of this form**

SECTION ONE

1. Appointment/position held by applicant and Division within FHM PhD Student

2. Contact information for applicant:

E-mail: [redacted] **Telephone**: [redacted] (please give a number on which you can be contacted at short notice)

Address: [redacted]

3. **Names and appointments of all members of the research team (including degree where applicable)**

Alex Bates – PhD Student

Professor Ceu Mateus, Division of Health Research

Dr Sam Clark, Senior Lecturer, Division of Politics, Philosophy and Religion

3. If this is a student project, please indicate what type of project by marking the relevant box/deleting as appropriate: (please note that UG and taught masters projects should complete **FHMREC form UG-tPG**, following the procedures set out on the FHMREC website

PG Diploma ☐ Masters by research ☐ PhD Thesis ☒ PhD Pall. Care ☐

PhD Pub. Health ☐ PhD Org. Health & Well Being ☐ PhD Mental Health ☐ MD ☐

DClinPsy SRP ☐ [if SRP Service Evaluation, please also indicate here: ☐] DClinPsy Thesis ☐

4. Project supervisor(s), if different from applicant:

5. **Appointment held by supervisor(s) and institution(s) where based (if applicable)**:

SECTION TWO

Complete this section if your project involves existing documents/data only, or the evaluation of an existing project with no direct contact with human participants

1. Anticipated project dates (month and year)
Start date: February 2021 *End date: January 2022*

2. Please state the aims and objectives of the project (no more than 150 words, in lay-person's language):

Currently, when the NHS assesses how valuable a new medicine is it assumes that the best possible outcome is to restore a diseased person to a non-diseased state. However, it is possible to imagine medicines which improve on this and offer 'better-than-perfect' health, for example by gene editing children to select for increased happiness. If medicines can theoretically add unlimited amounts of health, the NHS' current position is that they would pay unlimited amounts of money for it, potentially transferring resources away from the sick and towards those who can benefit from this new technology. This PhD study will create a mathematical model of this problem and identify which (if any) responses from bioethicists resolve the issue. It is hoped that the data from these three phases will inform the response of NICE and other regulators to the emerging issue of 'better than perfect' healthcare technologies in a health technology appraisal context.

Data Management

For additional guidance on data management, please go to Research Data Management *webpage, or email the RDM support email:* rdm@lancaster.ac.uk

3. Please describe briefly the data or records to be studied, or the evaluation to be undertaken.

The data will consist solely of publicly available documents, and more specifically will consist of National Institute for Health and Care Excellence evaluations of a selection of technologies where elements of 'better than perfect' health will have had to have been discussed by the committee. These documents will describe the economic reasoning leading to the decision which was made. The economic models will be replicated from the description of these models in the report. (To avoid duplication of effort, the original economic models will be requested from NICE if they are still available; these models are not available to download but are available to the public on request).

Once obtained, the evaluation will consist of amending the economic model to allow robust consideration of various philosophical positions on 'better than perfect' health described in my thesis. The different approaches will be explored and variations in outcome will be highlighted. The ultimate intention is to identify if any single approach can consistently be used by HTA agencies when assessing 'better than perfect' healthcare technologies.

4a. How will any data or records be obtained?

Publicly available data will be downloaded. If any non-public data is required (for example statistical CODA from indirect treatment comparison analysis) the original authors will be contacted by email.

4b. Will you be gathering data from websites, discussion forums and on-line 'chat-rooms' n o

4c. If yes, where relevant has permission / agreement been secured from the website moderator?

N / A

4d. If you are only using those sites that are open access and do not require registration, have you made your intentions clear to other site users? N / A

4e. If no, please give your reasons N/A

5. What plans are in place for the storage, back-up, security and documentation of data (electronic, digital, paper, etc)? Note who will be responsible for deleting the data at the end of the storage period. Please ensure that your plans comply with General Data Protection Regulation (GDPR) and the (UK) Data Protection Act 2018.

During the project phase, all data will be stored electronically on Lancaster University's OneDrive, with a backup copy stored locally on the hard drive of the workstation where I intend to do most of my analysis. My advisor will have access to data stored on OneDrive.

The analytical files (for example Excel or R files) will be maintained in a similar fashion, except that care will be taken to ensure a good audit trail using archiving techniques. If output files are too large to reasonably be stored with the model, these will also be stored in a similar fashion alongside a codebook explaining the variable and value labels.

Raw and analytical data will be stored by the principle investigator for a minimum of 10 years. If I am no longer affiliated with the University, access to the OneDrive subdivision where the data are stored will be transferred to my supervisor.

6a. Is the secondary data you will be using in the public domain? y e s

6b. If NO, please indicate the original purpose for which the data was collected, and comment on whether consent was gathered for additional later use of the data.

N/A

Please answer the following question *only* if you have not completed a Data Management Plan for an external funder

7a. How will you share and preserve the data underpinning your publications for at least 10 years e.g. PURE?

All data will be made available in an electronic format on the journal website of all publications based on the data. The data will also be deposited in Lancaster University's institutional data repository (PURE) and made freely available.

7b. Are there any restrictions on sharing your data?

No

8. Confidentiality and Anonymity

a. Will you take the necessary steps to assure the anonymity of subjects, including in subsequent publications? N/A

b. How will the confidentiality and anonymity of participants who provided the original data be maintained?

No subject data will be collected; all analysis will be of documents in the public domain or of unpublished economic models described in those documents.

9. What are the plans for dissemination of findings from the research?

The results will initially be published in the form of a PhD thesis. Individual elements of the project may also be suitable for publication in a peer reviewed journal or academic conference. It is also hoped that the publication of the research could start a dialogue with NICE on the appropriate method of handling the issue of 'better than perfect' healthcare technologies.

10. What other ethical considerations (if any), not previously noted on this application, do you think there are in the proposed study? How will these issues be addressed?

The research itself does not involve human subjects, and therefore the research in itself is unlikely to create any ethical issues. However, it is possible that the results of the study might impact the way that NICE assess a certain class of healthcare technologies, leading to benefit for some patients and harm to others. It is expected that the net benefit is likely to be positive, but this is still an important ethical consideration. Furthermore, if an error is found in the original NICE economic modelling then I

would have an ethical obligation to report this, and it is possible that patient treatment might be impacted by the resulting re-analysis

SECTION THREE

Complete this section if your project includes *direct* involvement by human subjects

N/A

SECTION FOUR: signature

Applicant electronic signature: [redacted] Date 12/10/20

Student applicants: please tick to confirm that your supervisor has reviewed your application, and that they are happy for the application to proceed to ethical review ☐

Project Supervisor name (if applicable): Ceu Mateus Date application discussed

Submission Guidance

1. **Submit your FHMREC application by email to Becky Case (**fhmresearchsupport@lancaster.ac.uk) as two separate documents:
   i. **FHMREC application form.**
   Before submitting, ensure all guidance comments are hidden by going into 'Review' in the menu above then choosing *show markup>balloons>show all revisions in line.*
   ii. **Supporting materials.**
   Collate the **following materials for your study, if relevant, into a single word document:**

a. **Your full research proposal (background, literature review, methodology/methods, ethical considerations).**
b. Advertising materials (posters, e-mails)
c. Letters/emails of invitation to participate
d. Participant information sheets
e. Consent forms
f. Questionnaires, surveys, demographic sheets
g. Interview schedules, interview question guides, focus group scripts
h. Debriefing sheets, resource lists

Please note that you DO NOT need to submit pre-existing measures or handbooks which support your work, but which cannot be amended following ethical review. These should simply be referred to in your application form.

1. Submission deadlines:
    i. Projects including direct involvement of human subjects **[section 3 of the form was completed]**. The *electronic* version of your application should be submitted to Becky Case **by the committee deadline date.** Committee meeting dates and application submission dates are listed on the FHMREC website. Prior to the FHMREC meeting you may be contacted by the lead reviewer for further clarification of your application. Please ensure you are available to attend the committee meeting (either in person or via telephone) on the day that your application is considered, if required to do so.
    ii. The following projects will normally be dealt with via chair's action, and may be submitted at any time. **[Section 3 of the form has *not* been completed, and is not required].** Those involving:
        a. existing documents/data only;
        b. the evaluation of an existing project with no direct contact with human participants;
        c. service evaluations.

3. <u>You must submit this application from your Lancaster University email address, and copy your supervisor in to the email in which you submit this application</u>

Appendix F. Full list of references

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