Improved methods and actionable tools for enhancing HTA

D11.2: Stakeholders' perspective: a political economy report

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Content

General introduction

European health systems today face significant health care expenditures increases[1] [2]. This trend will continue in the coming years supported by various factors. Due to the combination of low fertility rates and increasing life expectancy, European countries face an ageing population[3]. This change in the population composition will lead to an increase in chronic and degenerative diseases raising the demand for health care expenditures. According to an OECD report[4], the over-65 age group accounts for 40-50% of healthcare spending. Moreover, health care being a superior good, the increasing living standards in Europe raise expectations regarding health care[5] [6]. Finally, the development of innovative technologies combined with weak cost-containment measures, is a major factor in rising health care costs[7] [8]. According to OECD forecasting, health spending per capita will grow at an

[1] According to the OECD definition, health expenditure measures "the final consumption of health care goods and services (i.e. current health expenditure) including personal health care (curative care, rehabilitative care, long-term care, ancillary services and medical goods) and collective services (prevention and public health services as well as health administration), but excluding spending on investments".

[2] Pammolli, F., Riccaboni, M., & Magazzini, L. (2012). The sustainability of European health care systems: beyond income and aging. The European Journal of Health Economics, 13(5), 623-634.

[3] Christiansen, T., Lauridsen, J., Nielsen, P.: Demographic changes and aggregate health-care expenditure in Europe. ENEPRI Research Report, No. 32 (2006).

[4] European Commission (2006). The impact of ageing on public expenditure: projections for the EU25 Member States on pensions, health care, longterm care, education and unemployment transfers. The report of the Economic Policy Committee and the Directorate General. Available from: http://www.worldbank.org/en/news/feature/2013/01/17/the-eu-11-in-an-aging-europe

[5] Robert E. Hall, Charles I. Jones, The Value of Life and the Rise in Health Spending, The Quarterly Journal of Economics, Volume 122, Issue 1, February 2007, Pages 39–72, https://doi.org/10.1162/qjec.122.1.39

[6] Okunad AA, Murthy VN. Technology as a 'major driver' of healthcare costs: a cointegration analysis of the Newhouse conjecture. J Health Econ. 2002;21: 147-59. [PMID: 11852912]

[7] Bodenheimer, T. (2005). High and rising health care costs. Part 2: technologic innovation. Annals of internal medicine, 142(11), 932-937.

[8] J.P. Newhouse Medical care costs: how much welfare loss? Journal of Economic Perspectives, 6 (1992), pp. 3-21.

average annual rate of 2.7% across the OECD and will reach 10.2% of GDP by 2030[9]. This health care expenditures increase takes place in a context of tighter budgetary constraints placed on public funding. Health care spending across OECD represented on average 8.8% of GDP[10], compared to about 5% for educational institutions from primary to tertiary levels[11]. This raises concerns about financial sustainability[12], as addressed in a recent OECD report[13].

In healthcare, as in other publicly funded services, decision-makers have to allocate scarce public resources. They often face challenging priority-setting dilemmas urging them to choose the most effective interventions. Health technology assessment (HTA) bodies can support decision-making by providing recommendations on the value of new health interventions (such as screening or drugs) compared to usual care. Many countries have identified their principles for priority-setting according to the values and principles specified at the EU level. However, practical ways in which these values and principles become a reality in the health systems of the EU vary significantly between Member States (MS). This is particularly true when deciding which goods and services should be included in the healthcare basket and the mechanisms used for their funding and provision.

Cost-effectiveness analysis is a common method used in economic evaluation. Healthcare interventions are usually classified into four quadrants where differences in costs are reported on the y-axis and differences in medical efficacy on the x-axis. Most health technology assessments and policy decisions about pricing and reimbursement (P&R) deal with interventions located in the N-E quadrant, namely incrementally cost-effective interventions, implying both higher costs and higher efficacy gains compared to usual care. Conversely, interventions located in the S-W quadrant, i.e. allowing cost-savings at the price of a reduction in clinical efficacy, are qualified as decrementally cost-effective interventions (hereafter d-CEIs). Some of these interventions have been found to be highly effective, as shown by the systematic literature review carried out as a first step of this

[9] Lorenzoni, L., Marino, A., Morgan, D., & James, C. (2019). Health Spending Projections to 2030: New results based on a revised OECD methodology.

[10] OECD health statistics 2020.

[11] OECD.(2019). Society at a Glance 2019: OECD Social Indicators, OECD Publishing, Paris. https://doi.org/10.1787/soc_glance-2019-en

[12] Clements, B. J., Coady, D., & Gupta, S. (Eds.). (2012). The economics of public health care reform in advanced and emerging economies. Washington, DC: International Monetary Fund.

[13] OECD (2015). Fiscal sustainability of health systems: bridging health and finance perspectives, https://dx.doi.org/10.1787/9789264233386-en

research, but are rarely recommended or adopted. In a context of increasingly limited resources, d-CEIs could offer a powerful lever as the savings generated by substituting from usual care to d-CEIs could be reallocated to increase the overall health of the population, thereby complying with values and principles shared by most European health systems: *universality, access to good quality care, equity*, and *solidarity* (2006/C146/01).

Nevertheless, d-CEIs' potential remains undervalued and they have received much less attention from HTA bodies than incrementally cost-effective interventions (i-CEIs). For instance, d-CEIs are not explicitly mentioned as such in the EUnetHTA *core model for screening technologies*, established and funded by the EU, in order to contribute towards a more homogenous presentation of productions by MS HTA bodies. In cases of both lower costs and lower clinical effectiveness (SW quadrant), the core model suggests that further analysis is necessary before deciding on adoption. In fact, based on its incremental cost-effectiveness ratio (ICER), a d-CEI should be considered cost-effective if the society considers that the cost savings compensate for the lower effectiveness (EUnetHTA, 2011). How society may consider that the cost savings indeed compensate for the lower effectiveness is however, not addressed in the core model.

The main research question addressed in this report is, therefore, under which conditions will a decision-maker consider, and possibly adopt a d-CEI. It bridges over to the more general issue of the relationship between individual and collective benefits. Should the collective interest override the individual interest? In order to document this societal issue, economists must work closely with other disciplines, philosophy and ethics, but also public health (health policy) and psychology. Such is the strategy adopted here, by bringing on board the ethical perspective and using methods from behavioural economics to study individual and collective preferences.

The first part of this report offers a thorough micro-economic analysis of d-CEIs in order to identify their distinctive characteristics and their welfare properties. It focuses on one of the most central questions, namely the symmetry between willingness to accept and willingness to pay, and addresses the controversy of the slopes of the thresholds in the N-E and S-W quadrants. The second part consists of an inquiry into the ethics of d-CEIs. It questions the validity of the justification often used by policy-makers for not considering d-CEIs: their unethical nature. The third part analyses health policy in the making, by documenting HTA bodies' willingness to adopt d-CEIs whose cost-effectiveness has been scientifically established. The fourth part of this report presents the quantitative and qualitative results of the discrete choice experiment specifically designed for this research project. The conclusion offers recommendations to foster appropriate and acceptable d-CEIs' adoption and introduces the policy tools developed in the last deliverable of WP11 (D11.3).

1- A micro-economic inquiry

This inquiry aims to provide a discussion on some fundamental aspects of d-CEIs from a micro-economic perspective and it is divided in 5 sections. The first section discusses the role of d-CEIs as a disinvestment strategy. The second section briefly presents the main concepts and principles in cost-effectiveness analysis (CEA) and its use in health technology assessment (HTA). The third section examines the decision rules in a decrementally-cost effective case. The fourth section discusses Cumulative Prospect Theory (CPT) and the controversy on the shape of thresholds ('the kinked threshold'). The fifth section studies the health equity dimension of d-CEIs.

1.1 – Decrementally cost-effectiveness interventions as a disinvestment strategy

Investing in a health technology represents an opportunity cost for the society; money allocated to an intervention cannot be allocated elsewhere. The decision-makers must therefore take decisions concerning the allocation of resources. Disinvestment is the act of "*withdrawing health resources from any existing health care practices, procedures, technologies or pharmaceuticals that are deemed to deliver little or no health gain for their cost, and thus do not represent efficient health resource allocation*" (Elsaug et al. 2007). It has increasingly been introduced after the financial crisis to reduce unnecessary, ineffective, inefficient, or harmful care. For example, the National Institute for Health and Care Excellence (NICE) - the UK's health technology agency body-has encouraged commissionaires to engage in disinvestment (UK rationing report). The OECD has also encouraged disinvestment in obsolete technologies and the mandatory use of HTA to evaluate the effectiveness of interventions with the ultimate goal of tackling wasteful spending on health. The OECD highlights that "disinvestment" from low-value technologies could be a powerful approach, since it contributes to limiting or removing the government funding for ineffective technology. "*Low-value care comprises ineffective care, i.e. interventions not proven to bring clinical value, and interventions for which the risk of harm exceeds the likely benefit"* (OECD, 2019, p.101).

Harris et al. (2017) suggest three main areas of opportunity for disinvestment 1) [Interventions] in current use that were not evaluated rigorously prior to their introduction and have subsequently been identified as unsafe, ineffective or not cost-effective; 2) existing [interventions] that are safe, effective and cost-effective but which have alternatives offering more significant benefits;3) [interventions that are overused or misused (Harris, C et al. 2017). Disinvestment could simply be the *"removal, reduction or restriction of any aspect of the health system for any reason*", just like the term "investment" only reflects a resource allocation process or the introduction, continuation or expansion of any aspect of the health system for any reason (Harris et al. 2017).

From an economic point of view, it is essential to integrate the notion of efficiency to the concept of disinvestment, especially when its purpose is to contribute to healthcare priority setting. In this context, d-CEIs are a powerful lever for disinvestment which HTA agencies and decision-makers may be willing to use. However, d-CEIs are, by nature, more challenging to implement, despite the evidence of being more cost-effective, because of the implied potential losses in health, however small.

1.2 - Evaluation techniques to account for benefits and costs of health interventions

Scarcity is a central notion in economic thinking. A tension arises between unlimited wants (e.g. a patient with unlimited needs) and limited resources (e.g. number of physicians, available beds in hospitals) to satisfy them. In a context characterized by scarce resources, how can the health care sector best allocate resources for patients? Which new technology should be adopted? Decision-making within the health care sector is thus constrained by budgets. Economic evaluation enables the analysis of and comparison across different interventions by assessing both the costs and benefits derived from resource allocation decisions.

Any decision in health care provision entails an opportunity cost. This central concept in economic means that a given choice to allocate resources within the health care system is invariably linked to sacrificing another possible allocation. Therefore, from an economic point of view, it is essential to understand to which extent a health care intervention improves population health and minimizes opportunity costs. Economic evaluation aims to provide robust information for decision-makers so that resources can be targeted to those interventions that yield the highest benefits.

Two main techniques are used to evaluate costs and benefits in the literature: cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) (Palmet et al 1999, Sculpher & Price 2003). These approaches differ in the way that benefits are accounted for. CBA values the health outcomes in terms of monetary gains/losses. However, due to the difficulty in assigning a monetary value to health outcomes, CBA is rarely used (Bergmo, 2015). In CEA, benefits are represented as changes in health outcomes. It identifies which interventions produce the highest benefits at the lowest possible cost. The costs, expressed in monetary units, are compared to health outcomes. There are two main types of CEA: standard CEA and cost-utility analysis (CUA). In standard CEA, the costs are compared to a one-dimensional unit of effect. This could be blood-pressure or hemoglobin levels, number of symptom-free days, etc. When comparing interventions related to the same health problem, CEA may be the most suitable candidate to carry out economic evaluation (Bergmo, 2015). For instance, if the objective of adopting non-drugs interventions (e.g. improving diet or increasing

physical activity) in diabetes care is to reduce and stabilize blood glucose levels, it seems appropriate for the end point to measure blood glucose levels. However, it may not be easy to interpret measures in terms of cost per reduction in blood glucose.

In CUA, the outcome is measured as "healthy years" and valued as, for example, quality-adjusted life years (QALYs). The QALY is a measure that combines quantity and quality of life into one metric, allowing analysts to compare changes in health status both within and across conditions. The commonly used form, also known as the conventional QALY, was developed to inform societal resource allocation decisions across various healthcare interventions (Carlson et al 2020).

In both CEA and CUA, comparisons are made between two or more interventions. Figure 1.1 shows the typical structure of the analysis for two interventions. The standard care costs are denoted C_1 and yield an outcome (benefits) of E_1, while the new intervention costs are denoted C_2 and produce an outcome of E_2.

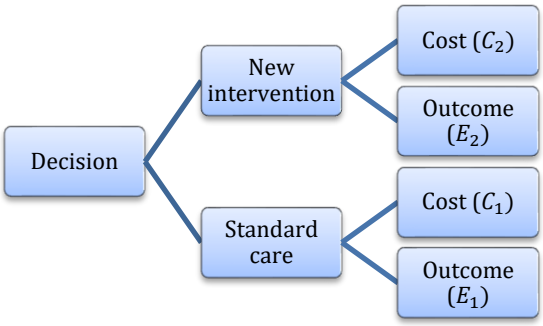


Figure 1.1. Structure of cost effectiveness analysis comparing two interventions

The opportunity cost of the new intervention is reflected by comparing it with the next best alternative, which is typically, but not always, current standard care. A cost effectiveness plane is drawn to then graph the incremental effectiveness and incremental costs. This plane is divided into four quadrants, as shown in figure 2.2, with the origin indicating the position of the comparator (most often, standard care). Incremental costs are most often on the vertical axis and the incremental effectiveness on the horizontal one. The North-West and South-East quadrants are known as the "no-brainer" solutions. In the former, the new treatment is less effective and costlier, therefore the existing treatment dominates. In the latter, the new intervention costs less and yields higher benefits. If the new treatment is located in the North-East quadrant, it means that it is both more effective, but also costlier (i.e. incremental cost-effectiveness). By symmetry, in the South-West quadrant, the new treatment is both less costly and less effective (i.e. decrementally cost-effectiveness).

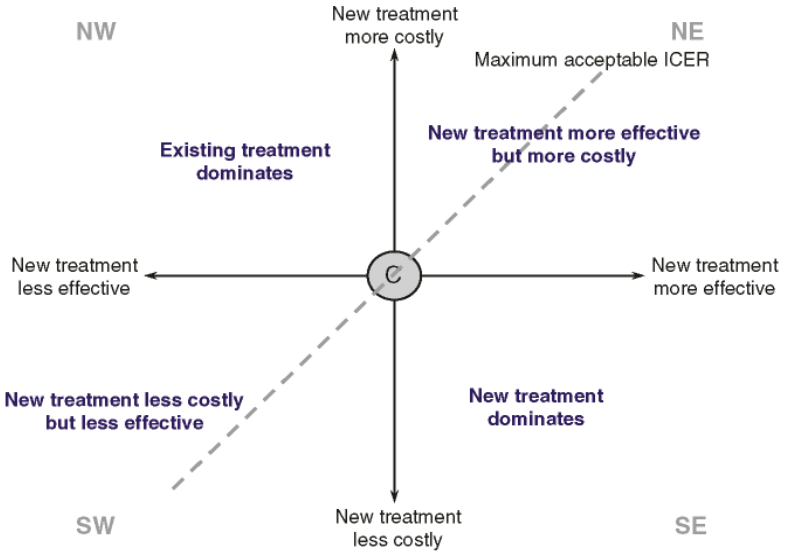


Figure 1.2. Structure of cost-effectiveness analysis comparing two interventions

Situations located in the North-East and South-West quadrants require additional analysis. Considering that the main objective of a health care system is to increase the value provided through its services to the final users, the patients, an intervention delivers high-value, where value is measured as the benefits obtained by patients per euro spent, if the health benefits justify the costs above a certain threshold, represented by a dotted line in figure 2.

Mathematically, this can be defined by the Incremental Cost-Effectiveness Ratio (ICER):

$$ICER = \frac{C_1 - C_0}{Q_1 - Q_0} = \frac{\Delta C}{\Delta Q}$$

Where Q_1 and $C_1$are the health effects and costs of the new intervention, while Q_0 and C_0 represent the health effects and costs of the comparator. In a decrementally cost-effective intervention (d-CEI), the costs represent the health foregone and the benefits are the cost savings. Understanding when an intervention is too expensive is probably the most difficult task for decision-makers.

1.3 - Decision rules in decrementally-cost effective situations

Healthcare expenditures place a high burden on public revenue. Demand factors such as an ageing population and increasing living standards raise the population expectations regarding care. On the supply side, new technologies are constantly being developed but they often imply a very high price.

These costs are not necessarily in line with health gains, so society must ask when such technologies are "too expensive". For that reason, it is relevant to analyse displacement strategies by examining the full costs and benefits of new technologies. This is a useful tool for decision-makers to understand under which conditions the savings derived from adopting a d-CEI become acceptable.

In this section, we present the rules that define an optimal allocation of resources for a decision maker constrained by a given -fixed- budget[14]. From an economic perspective, the point at which something becomes too expensive is related to the objective function of a decision maker and his constraints. The objective function is determined by the approach used by the decision-maker, whether his goal is to maximize overall wealth (welfarist approach) or simply health (extra-welfarist approach). The aim of the welfarist approach to maximise societal welfare, where the threshold represents the shadow price of overall wealth, since it includes the foregone health and consumption. Complementary, the extra-welfarist approach is more focused in its scope, since it only maximizes health effects in a resource-constrained health system, and thus the threshold is interpreted as the shadow price of health.

After the 1980s, the consensus favours the extra-welfarist approach, under the argument that it is easier to operationalize in healthcare. This consensus is explained by the increase in the number of HTA agencies and the development of key metrics, such as QALYs.

An increased demand for health economics evidence, an increase in the number of health technology assessment (HTA) agencies, and the development of such key metrics all contributed to this shift (Buchanan and Wordsworth, 2015). The extra-welfarist approach is followed by major decision-makers, including the National Institute for Health and Care Excellence (NICE) in the UK, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Canadian Agency for Drugs and Technologies in Health (CADTH).

1.3.1 - Welfarist perspective

In the context of the broader societal perspective, the decision rule, firmly rooted in welfare economics (e.g. Meltzer 1997), can be written as:

[14] The allocation is optimal in the sense that no greater level of health effectiveness could be obtained at a lower cost to the decision maker. Effectiveness may be expressed either in natural units (such as years of life gained) or in measures that incorporate both survival and quality of life (such as quality-adjusted life years gained or healthy years equivalents gained).

$$V_Q \Delta Q - \Delta c_t > 0$$

Where V_Q denotes the consumption value of health, ΔQ the decremental loss in health (thus ΔQ <0) and Δc_t the decremental total costs. Note that Δc_t denotes the total of both health care costs (Δc_h) and broader consumption costs (Δc_c), so that $\Delta c_t = \Delta c_h + \Delta c_c$. The last equation can be rewritten as:

$$(\Delta c_t / \Delta Q) > V_Q$$

This equation shows the ICER on the left-hand side and simply states that the savings due to the decremental costs per lost unit of health benefit (QALY) should exceed the consumption value of this unit of health benefit. Hence, in this decision context, V_Q is the relevant threshold determining when something becomes too expensive.

1.3.2 - Extra-welfarist perspective

Using the same notation, the decision rule related to the narrower health care perspective, assuming a fixed health care budget, can be written as:

$$k \Delta Q - \Delta c_h > 0$$

where *k* is the marginal cost-effectiveness of current spending in the health care system and only health care costs (Δc_h) are considered. Ideally, *k* represents the cost-effectiveness ratio of the interventions that get displaced (given the fixed budget) because of funding the new intervention (*k* = $\Delta c_{hd} / \Delta Q_d$). The previous equation can be rewritten as:

$$\frac{\Delta c_h}{\Delta Q} > \frac{\Delta c_{hd}}{\Delta Q_d}$$

This simply means that the cost-effectiveness of the new intervention should be greater than the cost-effectiveness of the displaced care.

1.3.3 - Mixed approach

In principle, one would expect *k* to be equal to V_Q, as this theoretically would yield an optimal budget for health care. Whenever the health care budget is fixed and non-optimal (so that $k \neq V_Q$), *k* will be relevant next to V_Q, also in the context of a broader societal perspective and maximizing welfare. The relevant equation for the broader societal perspective, which can still be extra-welfarist (Brouwer et al 2008), then becomes:

$$V_Q \left[\Delta Q - \frac{\Delta c_h}{k} \right] - \Delta c_c < 0$$

Note that when $V_Q = k$ the equation becomes the same as in the welfarist case. The previous equation indicates that the value of the net health loss (i.e. the losses due to displaced care) should be smaller than the consumption costs savings. If the displaced technology is also assumed to be associated with broader societal costs or gains (e.g. productivity costs or informal care), $-\Delta c_c$ should represent the net change of the new activity compared to the displaced activity (Brouwer et al., 2018). Given that the optimality of health care budgets has not been established, information on *k* and V_Q is required to determine whether or not an intervention is too expensive. Therefore, these two parameters are the two most crucial parameters that decision-makers should have at their disposal. Given their relevance, the next section discusses what is known about *k* and V_Q.

1.3.4 - About the thresholds k and v: a tale of two not well-known parameters.

Brouwer et al. (2019) claims that, compared to the estimations of costs and benefits on the left-side of the equations used for the decision rules, little has been done to study the right-side. This situation creates a dilemma: we have better estimates of incremental cost-effectiveness of new technologies, but still have fairly little idea about what to compare these figures to.

Although it is important to know the ICERs between different interventions, the final judgement of whether something is worthwhile requires knowledge of *k* and/or *v*, depending on the applied decision rule. Therefore, much research is needed to estimate the monetary value of the QALY and the cost-effectiveness of displaced health care, as we are with the estimation of ICERs.

Ryen and Svensson (2015) presents a review of the literature about the monetary value of the QALY (e.g. *v*), which points out a large variation in the estimates, with an average around 75,000 euros. An interesting finding in this study is that the estimate depends on the size of the gain and it is higher for life extensions than for quality of life improvements. As pointed by Brouwer et al. (2020, p. 177), the latter issues not only raise questions about the relationship between willingness to pay (WTP) for health gains and the QALY model, but also the appropriate perspective to take in order to find *v*.

In some countries, *v*-thresholds depend on some key attributes, like disease severity. For example, in the Netherlands, for treatments targeted to diseases that cause large health losses, a threshold equal to €80,000 is used (Reckers-Droog et al., 2018). On the contrary, for less severe diseases, the *v-threshold* is lower, going down to €20,000 in case of mild diseases (and even zero for very mild diseases—implying that treatments for very mild diseases should not be publicly funded).

Estimates about the marginal cost-effectiveness of current health spending, *k,* vary of course between countries, since it depends on the efficiency with which the healthcare system translates resources into health outcomes. This is usually done by considering the (average) marginal gains of

increased health care spending. There is a large variation in k estimates: in the UK, the *k*-threshold is estimated between £13,000 and £17,000 (Claxton et al., 2015b), while in Netherlands it is around €41,000 (van Baal et al., 2019), and €23,000 in Spain (Vallejo‐Torres et al., 2018).

As discussed by Brouwer et al. (2019), *k* and *v* thresholds in the literature show a discrepancy in their values. Such differences have several implications worth discussing. First, given that *v* is a threshold which has equity elements imbedded in its estimation, it is essential to know the relative distribution of different "equity types" of QALY gains for decision-makers, in order to compare *v* to *k*. For instance, it is important to know if interventions are targeted at areas with a high, average or low "equity-weight". Consider the Netherlands case, the *k*-threshold equal to €41,000 is in the *v*-threshold range (between 80,000 and zero), thus *k* implies the value of health gains with an "average" equity weight or value. Second, the estimates for *k* are based on public funds and thus they have an implicit societal valuation of health gains. This makes *k*-*v* threshold comparisons more difficult to carry out, since v usually assumes an individual perspective.[15] A third point, which is particularly relevant for disinvestment decisions, is that the *k*-threshold is ultimately a population mean. In practice, healthcare interventions may be above or below such average. If cost-effectiveness is unknown for displaced interventions, *k* may be instead adopted. However, a decision-maker may well face a situation where displaced technologies exhibit large cost-effectiveness variations, in which case the *k*-threshold may yield a poor (or rather uncertain) reference point.

1.3.5 - Thresholds: Willingness to pay versus willingness to accept

There are two essential measures for healthcare in CEA: willingness to pay (WTP) and willingness to accept (WTA). WTP indicates the monetary value an agent is willing to pay in order to get access to a certain healthcare good or service. Willingness to accept refers to the monetary value an agent should be compensated for in order to forego a given healthcare good or service.

The cost-effectiveness plane suggests a direct application of WTP and WTA. As discussed previously, the decision rules derived from the cost effectiveness plane in the N-E and S-W quadrants depend

[15] An exception is Bobinac et al. (2013) who investigated societal valuations of health gains, and found that people were willing to pay up to €52,000 per QALY for gains in others (i.e. gains that would not accrue to themselves) and €83,000 per QALY when the gains were in either others or themselves.

on the threshold value which defines high-value care. The threshold in the N-E quadrant is equivalent to WTP, while the S-W threshold captures WTA.

Numerous empirical studies (both experimental and observational) support the hypothesis that, for the same good or service, there are substantial differences between the WTP and WTA. For instance, in a meta-analysis, Tunçel and Hammitt (2014) report an overall WTA/WTP ratio equivalent to 3.28, which means that, for agents to give up a good or service, they should receive a compensation 3.28 higher than what they are willing to pay in order to have access to the same good or service. This proportion varies according to different markets. For instance, when analysing environmental goods, the authors find a ratio equal to 6.23, the largest in the literature. For healthcare markets, Rottevel et al. (2020) find that the WTA/WTP ratios varied from 0.60 to 4.01, with means of 1.73 for 15 mean estimates and 1.58 for 9 estimates. Individual data obtained from six papers, covering 71.2% of the subjects included in the review, yielded an unadjusted WTA/WTP ratio of 1.86 (95% confidence interval 1.52–2.28) and a WTA/WTP ratio adjusted for age, sex, and income of 1.70 (95% confidence interval 1.42–2.02).

Based on standard economic theory, WTA and WTP should be the same when there are zero transaction costs, the good/service is divisible and the market is not saturated. When such conditions do not hold, WTA and WTP may differ. The size of this difference depends on income, the proportion of income that is spent on the good, and the income elasticity (Brookshire & Coursey 1987; Randall & Stoll 1980).

The difference between WTA and WTP has important implications for healthcare decision making. Consider for example reimbursement decisions. If indeed WTA exceeds WTP, a higher cost-effectiveness threshold should be used for decisions related to ending reimbursement as compared to a choice to start reimbursement. As discussed by Van De Wetering (2017), ending reimbursement is more difficult than not starting reimbursement in the first place, both for policy-makers and for the general public. Therefore, the discrepancy between WTA and WTP is essential for policy-makers in a context of investment vs disinvestment of healthcare goods and services.

In short, there are three explanations for the disparity between WTP and WTA. The first explanation is related to measurement error. A second argument is related to the inability to substitute money for a (public) good, either because of perfect complementarity or because of asymptotic

boundedness of the utility curve [16] (Rotteveel et al., 2020). Lastly, a third explanation comes from Prospect theory, developed by Kahneman and Tversky (1979, 1991), which analyses loss aversion and framing effects. Due to the large literature that has been developed in this field, the next section summarizes the most recent findings of Prospect theory applied to health and its implications for d-CEIs.

1.4 - Kinked thresholds in the cost-effectiveness plane

The discrepancies between WTP and WTA raise three important questions for decision-makers. First, should decision-makers take into consideration the asymmetry between WTA and WTP? Second, which arguments can be made to recommend (or not) the adoption of a different threshold for the S-W quadrant? And third, what are the overall implications for HTA? The next section will try to answer these questions by discussing the two most prominent points of view in health economics: cumulative prospect theory and Jack Dowie's arguments.

1.4.1 - Cumulative Prospect theory

This theory, originally proposed by Kahneman and Tversky (1979[17], 1992), is a critique of the traditional Expected Utility (EU) framework. Unlike EU, which assumes linear probabilities and agents performing their calculations based on final wealth, cumulative prospect theory (CPT) is based on a behavioural model that shows how people decide between alternatives that involve risk and uncertainty.

CPT is characterized by four key behavioural traits: 1) reference dependence; 2) loss aversion; 3) diminishing sensitivity; and 4) probability weighting.

First, in prospect theory, individuals obtain utility from gains and losses, which is measured in relation to some reference point, rather than from absolute wealth. That is, utility derived from a good is defined over differences from a reference point (RP), instead of over the overall consumption of that good. This implies that the marginal impact of a change in value diminishes with the distance from a relevant RP.

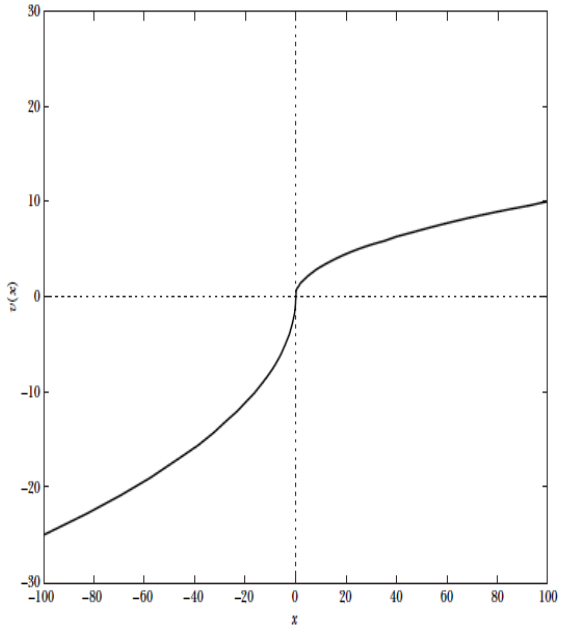
[16] Hanemann (1991) argues that the difference between WTA and WTP is proportionally related to the availability of substitute commodities. Therefore, the more agents lack potential substitutes, the larger the WTA–WTP differences.

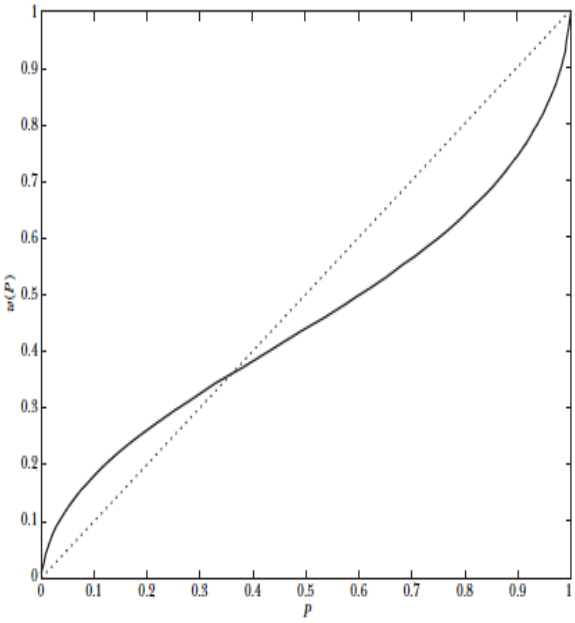
[17] Worth mentioning, this is the most cited paper ever to appear in *Econometrica*

Second, agents experience "loss aversion", which makes them much more sensitive to losses than to gains of the same magnitude. This implies that individuals typically require more compensation to give up something they own than they would have been willing to pay to obtain it in the first place.

The third refers to diminishing sensitivity. Notice that in panel (a) of figure 1.3, the function is concave in the gains' quadrant and convex in the opposite case, which implies that individuals are risk-averse in the former and risk-seeking in the latter.

And fourth, individuals do not evaluate outcomes based on objective probabilities. Instead they use weighted probabilities derived from the weighting function *w(p).* Panel (b) shows the weighting function. This graph contains a dotted line (e.g. 45-degree line that corresponds to Expected Utility theory benchmark) and a curve that is below a given threshold (in this case around p=0.35) is above the dotted line and, after that threshold, it is placed below that line. The interpretation of this graph is that individuals overweight small probabilities and underweight large ones. Kahneman and Tversky emphasize that the transformed probabilities π do not represent erroneous beliefs; rather, they are decision weights (Barberis 2013).





Panel (a) CPT value function

Source: Barberis 2013, p.176

Panel (b) Probability weighting function

Source: Barberis 2013, p. 177

Figure 1.3. CPT value function and probability weighting function

1 - Prospect theory in the health domain.

Economic evaluations are the main tool used by policymakers to allocate scarce healthcare resources, where health benefits are expressed in terms of utility. The common utility model used is the Quality-Adjusted Life-Years (QALY) model (Pliskin et al., 1980), which is based on expected utility (EU) theory. However, in the field of health economics, EU exhibits a number of violations that have been reported during the last decades (Bleichrodt et al., 2007; Llewellyn-Thomas et al., 1982; Treadwell and Lenert, 1999). This puts into question the empirical validity of the QALY model in its present form. CPT has been used as an alternative approach in health economics with more descriptive validity (Attema et al., 2013).

Traditionally, CPT has been studied in a context which involved monetary transfers and its main hypotheses have been widely confirmed by different studies. However, health may be a very different type of commodity[18] and thus one may ask how different health outcomes behave when we test CPT behavioral assumptions (e.g. probability weighting, reference-dependence, S-shaped utility function). This section presents the main findings on these questions in the economics literature.

2 - Testing CTP on health outcomes.

Bleichrodt and Pinto (2000) study the utility or probability weight for health outcomes. In their experiment, subjects were told that they suffered from one of two possible diseases, without being told which. The outcome of interest in this study is life duration. The authors obtained two main results. First, that there is significant evidence of probability weighting both at the aggregate and at the individual subject level. The modal probability weighting function is inverse S-shaped, displaying both lower subadditivity and upper subadditivity. Second, probability weighting is in particular relevant at the boundaries of the unit interval. Compared to studies involving monetary outcomes, authors find more elevation of the probability weighting function. An explanation for this finding may be that health is a more "affect-rich'' outcome than money.

What about loss aversion in health? Attema et al. (2013) estimate loss aversion in the health domain. The authors investigate this by using an application to life years. Their main findings confirm

[18] In contrast to money, from a methodological point of view, health outcomes are more challenging to study in CPT for two main reasons. First, health outcomes usually involve two attributes: longevity and quality of life (QoL). Second, QoL is a non-numerical attribute. Consequently, if we are to derive a full parameterization of the QALY model, we need to elicit values over both life duration and QoL.

two crucial CPT features in health: authors show loss and risk aversion for gains and losses, which for gains can be explained by probabilistic pessimism. This contrasts with the common finding of a convex utility for monetary losses. Life years are therefore different from monetary outcomes and need not generate convex utility for losses.

The authors provide five different explanations regarding the utility function for losses (Attema et al. 2013, p. 1063). First, if remaining life expectancy is very small, the situation can be comparable to that of being near "ruin", a point where utility for losses becomes concave. If loss of life duration is like "ruin", it becomes more natural to observe concave utility. Second, time preference generates enough concavity to more than offset the convexity due to diminishing sensitivity. Third, the decision problem may be understood by subjects as a situation of a delayed resolution of uncertainty. Fourth, subjects may have regarded zero remaining life years as their RP, and, hence, may not have considered any outcome as a loss. Lastly, people may have taken the certain outcome as their RP. This would imply that they have considered all prospects, both in the gain part, the loss part, and the mixed part, as mixed.

Complementary, Attema el al. (2016) investigates CPT by analysing QALYs as the main health outcome. Supporting previous findings in Attema et al. (2013), authors conclude that EU is violated for both health and monetary outcomes, with losses looming larger than gains and probabilistic pessimism. However, in contrast to Attema et al. (2013), Attema et al. (2016) results show that there is a deviation from the commonly observed *S-shaped* utility (reflection); instead of observing risk aversion for gains (i.e. concave utility function in the gains region) and risk-seeking behaviour for losses (i.e. convex utility function in the losses region), results show that utility is universally concave for the health outcomes in the study.

In the results of the WP11 discrete choice experiment (DCE) presented in section 4 of this report, our findings do not support the assumption of non-constant marginal valuations (e.g. either convex or concave WTA shapes), while a linear WTA threshold cannot be rejected.

3 - Incorporating risk aversion in health to CEA

Standard CEA models assume that consumers are risk-neutral in health (Garber and Phelps, 1997), which simplifies analyses but risks misrepresenting true consumer preferences.

Lakdawalla and Phelps (2020) depart from the original Garber and Phelps (1997) model. Let M_i be a composite medical spending in period *i* and $C_i \equiv Y - M_i$ the non-medical consumption. Define $H_i \in$ [0, 1] as QoL in period *i*. Period *i* utility is given by U(C_i)H_i, and the probability of survival to

period 1 is p_1. Expected utility is U$(C_0)H_0 + p_1U(C_1)H_1$. The optimal cost-effectiveness threshold is given by:

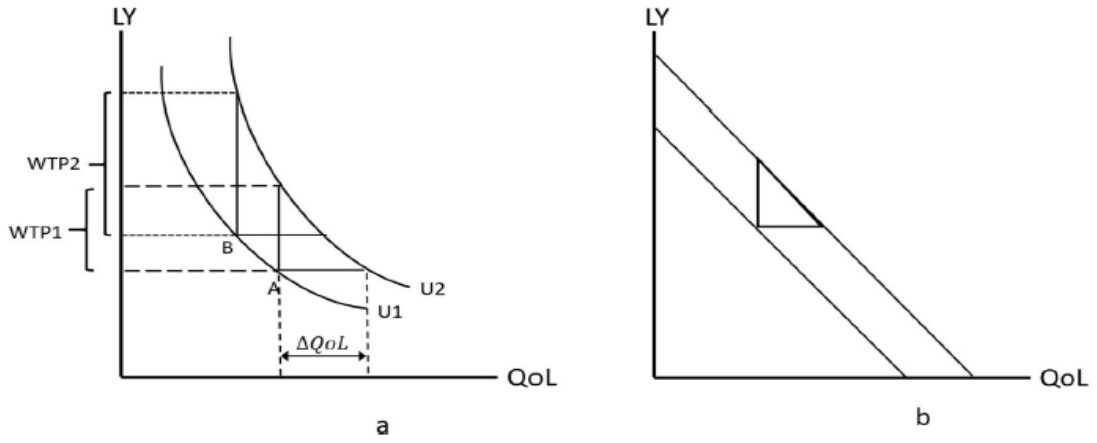
$$K = \frac{U(C_1)}{U'(C_0)}\left[\frac{1}{H_0}\right]$$

K reflects the value of future *QoL* gains paid for today and measured as consumption willingly foregone in exchange for one unit of *QoL*. H_1reflects the health status of patients when they require treatment. By assumption, H_1 incorporates the effects of the illness in question and, possibly, other unrelated disabilities[19] or illnesses. When individuals choose medical spending optimally, then *K* represents the cost-effectiveness ratio that leads to the first-best allocation of medical consumption. Contrary, if individuals face fixed-budgets, the resulting *K* turns into a suboptimal allocation. Lastly, for technologies that add Δp_1 in survival probability and H_1in *QoL*, *QALY* gains are defined as $\Delta QALY = \Delta p_1 H_1 + p_1 \Delta H_1$.

In contrast to Garber and Phelps (1997), who assume *LY* and *QoL* to be perfect substitutes, Lakdawalla and Phelps (2020) depart from a point of view where individuals have a taste for variety[20]. Such analytical assumption challenges the well-known results in CEA and known under '*a QALY is a QALY'.* This can be illustrated by the following compensating variation exercise. Consider point A on indifference curve U_1 in figure 1.4a, a fixed health gain of Δ*QoL* places the consumer on indifference curve U_2. The vertical distance WTP_1 (i.e. the compensating variation) returns the consumer to U_1 and measures (in life years *LY*) the value of this *QoL* gain. By following the same procedure in point B (starting at a lower QoL) we obtain WTP_2. Because of diminishing marginal utility of *QoL*, $WTP_2 > WTP_1$ for the same ΔQoL. This result is derived from a concave utility function. In addition, figure 1.4b illustrates preferences when utility is linear in both *LY* and *QoL*. In this case, *LY* and *QoL* are perfect substitutes (hence the conclusion that "a QALY is a QALY"), and indifference curves are straight lines. Thus, *WTP* for improvement in *QoL* is the same for all values of *QoL.*

[19] For example, physically disabled patients with diabetes would have lower values of H1 than patients with identical diabetes status but no physical disabilities.

[20] Imagine Consumer A, with nearly perfect *QoL*, but with only 6 months left to live. Consumer B has 5 years to live, but at *QoL* level 0.1. The linear indifference curves imply that these two consumers have identical willingness to trade away longevity in exchange for QoL. However, as discussed by Ladkawalla and Phelps, it it is possible to argue that Consumer B will have much greater interest in making such a trade.



Figure

Figure 1.4. Indifference curves for constant and diminishing marginal utility of QoL.

Source: Ladwalla and Phelps, 2020, p. 4

Once we allow for concavity, the implications are clear: the WTP threshold should be replaced by thresholds that increase as disease severity increases since risk-averse consumers derive greater value from health improvements when they face bleaker health prospects. Ignoring risk aversion over-values treatments for minor illnesses and under-values treatments for severe ones. Ladkawalla and Phelps empirical calibrations suggest that mild illness treatment might be over-valued by a factor of two to three, while severe illness treatment could be under-valued by up to an order of magnitude.

The implications for the S-W quadrant are straightforward and the answer will depend on the shape of WTA which depends on disease severity. These results are consistent with our findings in the DCE (section 4), where willingness to substitute usual care by a d-CEI decreased significantly when disease severity of the patient changed from low to moderate: the willingness to substitute decreased, on average, by 25%.

4 - Accounting for the reference point in HTA

Reference dependence is one of the fundamental principles of CPT. Within the context of studying health, the interpretation of the reference point may be subject to debate. As discussed by Attema et al. (2013, p. 1058), "*it is not so clear where the reference point lies for a health outcome as life years. One could argue that the RP is the expected remaining lifetime (e.g., using a mortality table or subjective life expectancy), the lowest outcome (Attema et al., 2012; Bleichrodt et al., 2001), the sure outcome (van Osch et al., 2004; van Osch and Stiggelbout, 2008) or the highest outcome in a choice*

situation, or that it depends on the goals of the respondents (van Osch et al.,2006). It is also likely to depend on the decision context and the framing of the questions." Therefore, the first point to note is that the RP is likely to be more heterogeneous among individuals in the health domain than in the monetary domain.

Attema el al. (2016) explored this issue by generating reference points by explicit framing and investigated how their manipulation affected preferences toward quality of life. More specifically, they conducted a direct test of traditional EU by investigating whether risk aversion is influenced by positioning of the reference point. The authors find more risk aversion when the same outcomes are framed as losses than when they are framed as gains. Such results appear contradictory with respect to other studies focused on monetary outcomes. In summary, the EU theory shows clear constraints to explain behaviour in health, suggesting that alternative theories accounting for sign-dependence are worthwhile.

The implications for the SW quadrant are important, if decision-makers want to pursue disinvestment strategies.

1.4.2 - Symmetric or kinked thresholds?

According to Dowie et al. 2015, the cost-effectiveness principle requires that the thresholds in the S-W and N-E quadrants be the same. The authors question the relevance of aggregated asymmetric individual preference estimates for group-level policy making, in the context of a resource-constrained system committed to equitable efficiency. Should individual preferences derived from a market context be reflected in public decision making?

To illustrate this point, the authors discuss the results in Grutters et al. (2008). Dowie et al. argue that the findings of the asymmetry between WTP and WTA mainly depended on how the cost attribute was framed, which, they argue, suggests that using a ratio different from 1 is unethical at a societal level. "*Searching for the conditions under which one or other framing should be used, which they contemplate, is inappropriate, since an equitable public policy requires an unbiased single estimate of WTP&A* (Dowie et al. 2015, p.6)."

If the public healthcare system is not willing to pay more than the given threshold for a new intervention, it can only be because the opportunity costs that will be imposed on all other patients in the system are judged to be greater than the benefits that will accrue to those who will receive the new treatment. Therefore, "*it would be irrational not to adopt a new technology that creates benefits to all other patients that will exceed those to the future anonymous patients who would otherwise be receiving the old intervention* (Dowie, 2005, p.2)." As argued by Severens et al. (2005),

from a welfarist perspective, decisions committed to cost-effectiveness as the ethical basis for resource allocation can remain coherent as long as they ignore irrelevant private preferences, as those derived from a kinked threshold. Ethical efficiency in a public health service can only be achieved with a fixed ICER threshold.

An example of such approach is used by the UK's National Institute for Health and Care Excellence (NICE). NICE decision-making context represents deliberative decision making on behalf of others, and affects only future treatment decisions without altering the healthcare of any individuals currently having a treatment. These aspects of the NICE decision-making context diminish the role of loss aversion, the endowment effect and status quo bias – and indicate that there may be little support for a discrepancy between willingness to accept and willingness to pay for coverage of specific health interventions with public sector funds.

Another problematic element in CPT is related to the non-linearity of the probability weighting function that individuals use in the maximization of utility. Dowie et al argue that "*the inability to relate emotionally to the loss of a relatively small amount of health by very large numbers, compared to the ability to relate to the gain of even a moderate amount for an identified individual – say one QALDay for 30,000 people compared with 1 QALY for one person - is to be treated as a problem to be addressed and overcome at the policy level, not to be automatically accommodated* (p. 5)."

According to Dowie et al. (2015), there are other practical implications to consider. The adoption of a different (kinked) threshold would place great importance on whether the intervention or the comparator represents the origin of the incremental cost-effectiveness plane. It would also require committees to interpret the same evidence on costs and health outcomes differently for review of existing HTA agencies interventions compared with appraisal of a new intervention. Thus, applying a single threshold to all decisions is consistent with maximising health gains from available resources. It represents a conservative approach to avoiding health losses, given the lack of evidence to support the need for or extent of any loss aversion or status quo bias in societal level decisions about health.

1.5 - Health equity trade-offs

Figure 1.5 shows a simplified representation of the potential trade-offs between equity and cost-effectiveness. The vertical axis shows the net total health impact (i.e. cost-effectiveness gains) while the horizontal axis represents the net health equity impact of an intervention. The equity impact depends on the equity metric used. At least three different equity metrics dimensions can be used, addressing different questions: 1) Equality of what? (e.g. Opportunity or costs); 2) equality of whom?

(e.g. individuals or particular groups); and 3) how do we measure equality? (e.g. relative or absolute indexes). (Kjellsson et al 2015; Asada et al 2015).

Quadrant I and III are the obvious interventions ("no-brainer" situations). If a policy-maker increases cost-effectiveness while improving equity, the intervention should be adopted. While if an intervention decreases cost-effectiveness and harms equity, the appropriateness of the intervention should be questioned. Quadrant II and IV represent the most interesting cases: quadrant II increases cost-effectiveness and reduces equity; quadrant IV shows a cost-ineffective intervention which improves equity.

In low and middle-income countries (LMIC), building a hospital may result in a situation where we observe losses both in terms of equity and efficiency (Asante et 2016). Investing in State-owned pharmacies which sells medicine at a cheaper price due to bargaining power may be located in the first quadrant (Atal et al 2021). Funding a particular medical technology may create efficiency gains but can increase inequality when there is low opportunity to access the healthcare system (quadrant II). Contrary to this situation, in quadrant IV, policies which intend to modify behaviours through preventive interventions may be cost-effective but could potentially increase inequality.

For instance, consider an intervention which aims to reduce the incidence of diabetes through the modification of lifestyle factors (e.g. increases in physical activity or healthy diet improvements), despite the fact it could indeed turn out to be a d-CEI, it may have higher impact on wealthier individuals, who tend to respond more readily to such interventions.

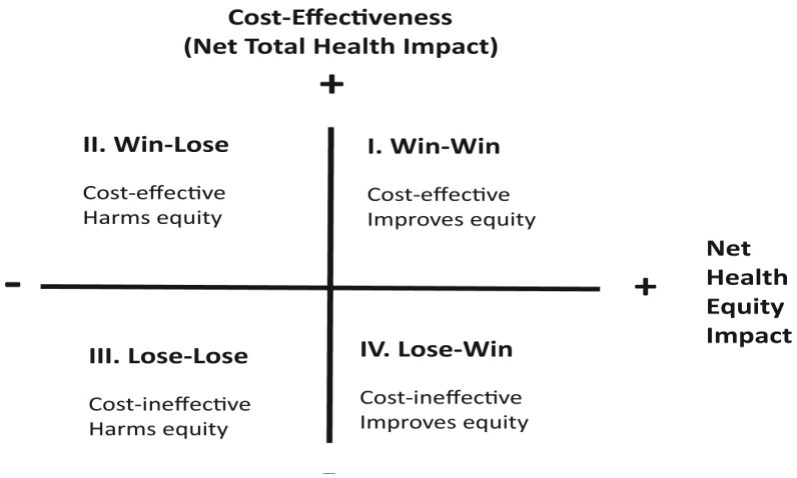


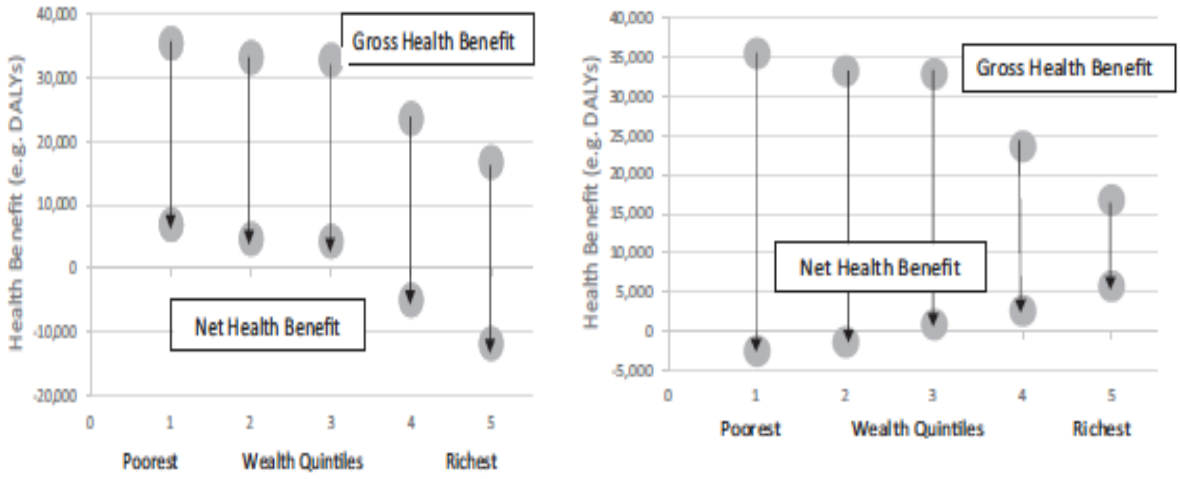
Figure 1.5. Health equity impact plane

Source: Cookson et al 2017

1.5.1 - Net equity impacts

When assessing equity impacts, both distributions of benefits and opportunity costs are important. For example, the lost health benefits derived from the comparator may be unequally distributed across the population (Norheim 2006). As mentioned by Cookson et al 2017 (p. 208), the distribution of opportunity costs will depend crucially on how a program is funded. For example, if an intervention is funded by increasing taxes in a progressive regime, the burden will be disproportionately paid by the rich. On the contrary, if such intervention is funded by reducing public expenditure on food stamp subsidies, the opportunity costs in terms of losses in health and well-being may be impacting disproportionately more the less advantaged households who tend to rely more heavily on such programs. Due to the disinvestment that occurs in d-CEIs, this is a crucial aspect to study.

Figure 1.5 shows the potential health equity implications of alternative sources of funding. The "gross" health impacts consider only the distribution of program benefits, as if there were no health opportunity costs. These gross impacts are shown as the upper circles in the diagram, representing the sum of the total population health gains generated by the program. Figure 1.6a illustrates a case in which the health opportunity costs are assumed to be equally distributed. Figure 1.6b illustrates a case in which funding comes from a program that disproportionately benefits socially disadvantaged groups. Figure 1.6b shows that programs that initially seem to have a pro-poor health equity impact may, in fact, be equity neutral or even anti-poor when one accounts for the health effects of diverting money from alternative uses.



Panel (a): Equal opportunity cost

Panel (b): Unequal opportunity cost

Figure 1.6. Health equity implications of opportunity costs: hidden traps.

Source: Cookson et al 2017

1.5.2 - Equity Impact Analysis

CEA can be used to analyse the distributional benefits and costs from displacement expenditures in the healthcare budget. In this section we summarize the three main approaches found in the literature.

1 - Extended cost-effectiveness analysis (ECEA)

This methodology was developed by the Diseases Control Priorities (-IP-3) project. ECEA examines both health benefits and financial risk protection benefits per monetary unit of expenditures.

This methodology can be particularly useful to LMIC countries with high incidence of out-of-pocket payments (Cookson et al, 2017). For instance, Verguet et al. (2016) study the impact of a 50% cigarette price increase in which they find that such tax would be pro-poor: life-years would be more concentrated on the poor than on the rich, and the financial risks would be mainly absorbed by the poorest quintile group, accounting for at least 70% of the total 2 billion dollars.

2 - Distributional cost-effectiveness analysis (DCEA)

This methodology was developed by the University of York. The approach aims to analyse the distributional effects while emphasizing the distribution to the health opportunity costs from displaced expenditures within a fixed healthcare budget (Asaria et al., 2016). DCEA has two main

features: 1) it allows evaluation of multiple inequality impacts on different subpopulations and compares magnitudes; and 2) it aggregates all costs and effects into a single metric of net health benefits. Cookson et al. (2017) do not recommend using an index. Instead they propose performing sensitivity analyses using different equity weights to explore the implications of different views on the appropriate trade-offs between efficiency and equity.

3 - Equity-weighting analysis

If a d-CEI falls in the "win-lose" or "lose-win" quadrant of the health equity impact plane, decision-makers have to choose between equity and efficiency. Equity-weighting can be used by policy-makers to analyse such trade-offs by quantifying the importance of equity in order to reject a cost-effective intervention which may have harmful impacts on equity. This is accomplished by using "equity weights" for health benefits that apply to people with different characteristics or using an "equity parameter" that quantifies the degree of concern for reducing health inequity versus improving total health (Cookson et al., 2017).

Conclusion

Ultimately, one of the goals of the healthcare systems is to increase value provided to its users. In this sense, d-CEIs are a meaningful way for decision-makers to achieve budgetary goals while efficiently allocating resources in healthcare. These interventions help the system to reduce low-value care by eliminating interventions whose cost is higher and whose effectiveness is lower than that of other options.

Decision-makers ought to determine the objective function, whether the goal is to maximize overall wealth (welfarist approach) or just health (extra-welfarist approach). This is of utmost importance since it determines the relevant threshold and it gives an appropriate understanding of the underlying opportunity costs, either focusing on a narrow sectorial approach where decision-makers only analyse the effects of an intervention within the healthcare system or having a wider understanding of the problem, where the point of view includes consequences for the whole of society.

Additionally, HTA agencies are required to have a clear understanding on the symmetry of thresholds.

Research on individual preferences indicate that WTA and WTP are empirically different due to the following phenomena: 1) reference dependence; 2) loss aversion; 3) diminishing sensitivity; and 4)

probability weighting. However, as argued by Dowie, any asymmetry in individual preferences for WTP versus WTA should not be reflected in public decision making.

Finally, d-CEIs can be approached by incorporating a multicriteria decision analysis with at least two decision criteria—improving total health and improving health equity—and could be embedded within a wider multicriteria decision analysis that encompasses further decision criteria. Different equity dimensions are to be considered: reducing inequalities in health related to income, ethnicity, gender or other social variables; concerns about prioritizing patients based on disease severity or rarity, including end-of life patients. Aligning the methods of CEA to address equity concerns is only one facet of the much larger question of how to design fair processes of decision-making that appropriately address equity concerns.

2- An ethics inquiry

Decrementally cost-effective interventions (d-CEIs) designate a subset of healthcare interventions with a positive relationship between the outcomes and the costs associated with their adoption. In incrementally cost-effective interventions, health outcomes will improve and costs will increase, while d-CEIs are associated with a decrease on the two dimensions. As a matter of definition, d-CEIs involve accepting to forego, to some extent, clinical gains (outcomes reduction) for the sake of monetary gains (costs reduction).

When the relationship between outcomes and costs is negative, there is no need to ponder before taking a decision. For example, when comparing two houses located in the same area, everyone would prefer the bigger and cheaper house compared to a smaller and costlier one. Conversely, we will accept to consider different alternative courses of action if we are offered the choice between a bigger costlier house (providing each family member greater space, thus maximizing comfort) or a smaller cheaper one (offering family members the prospect maximizing the resources they can use for leisure time). This is the typical cost-effectiveness plane, defined along two axes, with the *y*-axis (the vertical axis) for the difference in costs and the *x*-axis (the horizontal axis) for the difference in outcomes. The origin (denoted *0*) is defined at the intersection of the axes, dividing the plane into four quadrants: in North-West (higher costs, lower outcomes) and South-East (lower costs, higher outcomes) quadrants, the decision to reject or to adopt appears straightforward; in the North-East (higher costs, higher outcomes) and in South-West (lower costs, lower outcomes), the decision involves a trade-off between costs and outcomes.

From an ethical and philosophical point of view, it is relevant to draw a distinction between considering and adopting, namely between reasoning on a course of action and on its alternatives, and opting for, or rejecting, it. At the time of consideration, one can apply different heuristics, different (more or less formalized) ways of reasoning. The cost-effectiveness plane offers a description of the decision-making process, and of its underlying heuristics, in terms of arbitrating between two dimensions for maximizing a utility. The underlying question is, especially when it comes to arbitrating on the two dimensions negatively (i.e., reducing costs and outcomes), whether such a way of reasoning can apply in healthcare, as it can apply when buying a house or other goods and services.

The negative answer is appealing, while the response 'yes' can seem ethically suspicious. The immediate rejection of any possibility to consider – let alone to adopt – decrementally cost-effective strategies in healthcare would undermine, from an ethics perspective, the whole enterprise in WP11 to reveal decision-makers' willingness to ponder when considering cost-effective interventions in the

South-West quadrant. Empirical results obtained from the discrete-choice experiment run in this work-package would then either appear trivial (confirming the ethical rejection) or as self-confirming of an opposition between two economic- and ethical- paradigms of decision-making in healthcare.

This is the reason why the present inquiry will tackle general objection to decremental cost-effectiveness in healthcare. The argument is two-fold: first, it makes the case that it can be ethically licit for decision-makers to take d-CEIs into consideration in healthcare; second, it argues that this can be beneficial in health democracies, by widening the options and, more importantly from an ethical perspective, by fueling the process of making explicit the aims and the values underlying collective and individual choices in health.

The objective of this contribution is to identify ethical reference landmarks and guidance into the possible adoption of decremental cost-effectiveness in healthcare by:

- Defining a conceptual background for an ethically plausible approach to considering – and possibly adopting – d-CEIs in healthcare.
- Demonstrating the practicability of considering d-CEIs in healthcare by listing inferences and related heuristic tests through which one may safely infer the choice of adopting one rather than the other from the comparison between decrementally- and incrementally-cost-effective interventions.

☛ *Concepts and theories are paralleled with empirical results from the discrete choice experiment conducted in WP11, as an illustration of the relevance of ethics developments to the practice of making decisions in healthcare.*

To lay down the foundations of such a guidance, one needs to explore d-CEIs as a plausible option in the choice environment of decision-makers in healthcare, and especially to set aside seemingly obvious ethical objections to it. For the sake of conciseness, the argument develops step-by-step, allowing one to pinpoint and synthetically address main moral, epistemological, and ethical issues. Each one of these issues would deserve careful attention to address specific objections thoroughly; this can be further investigated in future research once the overall picture has been set-up, which is the focus of the present inquiry.

2.1- From the objection to different stances: should healthcare make an exception to cost-effectiveness considerations?

The easy side in the response to the objection to decremental cost-effectiveness as unethical in healthcare lies in the seminal article coining health economics. The counterargument to economic reasoning applied to healthcare that it would disregard ethics would be simply irrelevant. Kenneth J. Arrow, when defining the scope of his study on "medical care as the object of normative

economics", immediately focuses on the "specific differentia" of this domain (Arrow 1963). As part of these differences, Arrow mentions an "ethical compulsion" or a "collectivity-orientation" among other "nonmarket forces". In this view, the development of cost-effectiveness analysis in healthcare can appear as a method allowing one to reveal relevant trade-offs and hierarchize alternatives according to their outcomes and the resources involved, but not as a value-laden (axiological) stance on the nature of the healthcare domain. On the contrary, Arrow develops his approach to healthcare building on the identification of its specific characteristics that can vary the realm of acceptable trade-offs in health compared to other fields of application, explaining why in healthcare, for instance, "it is the general social consensus, clearly, that the *laissez-faire* solution for medicine is intolerable" (*Ibid.*).

The objection, or the invitation, to consider d-CEIs in healthcare cannot therefore be simplified as opposing those considering, and those disregarding, the ethics. It would be far more plausible to hypothesize that these two stances rely on two different *descriptions* of the ethics in healthcare. When using the word "descriptions" philosophically, the intent is to highlight the linguistic nature of our attitudes towards an object (Russell 1912), here healthcare; accordingly, defining a stance towards decremental cost-effectiveness in healthcare does not rely on a (supposedly direct) knowledge of characteristics of healthcare making it specific, but relies on the articulation of concepts, some of them being descriptive, other being normative. To say it in Russel-like terms, nobody talking about "the ethics" can claim he is doing so because *he*, undertone not his opponents, is "acquainted" with healthcare (Russell 1914). On the contrary, he like his opponents articulates concepts and defends a conception of the demands of ethics in this domain.

This involves that when responding "no" to the question of whether cost-effectiveness can apply in healthcare, one will need to distinguish and to articulate two assumptions, namely that "*health-related goods and services are different from other goods and services'*, on the one hand, and that "*the way we are making decisions ought to differ in health compared to other domains"*, on the other hand. Accordingly, he will hold the stance that "*cost-effectiveness, especially decremental cost-effectiveness, should not apply in healthcare*". The wording "should" is key here; to avoid a fallacy, the two descriptive ("*is"*) and normative ("*ought"*) assumptions cannot be held as being logically connected. Their articulation implies a value-judgement as to whether one may, or may not, reason in the same way in healthcare compared to other domains, and this value-judgement rests on a description of the ethics in healthcare. Health economists do likewise when defending the reverse stance.

It would be pointless to arbitrate between the two descriptions of ethics. It is enough to show that the two descriptions, especially the one backing the consideration of decrementally cost-effective interventions, are plausible in healthcare. Future research can investigate further on overlaps and compatibilities, as well as on reasonable disagreements and value conflicts, in specific situations. A rich and still active ethics literature (from philosophers or economists) exists with regard with the question of incremental cost-effectiveness in healthcare (for an overview: Brock, 2004; or as an example of current developments: Munthe, Fumagalli et al. 2021). The literature is still embryonal and programmatic about decremental cost-effectiveness (Kent, Fendrick et al. 2004 ; Antiel, Curlin et al. 2013; Kamm 2015 ; Feiring and Wang 2018). The present inquiry builds on these two complementary scholarly bodies of literature and can contribute to sketching a roadmap to future ethics discussions around decremental cost-effectiveness.

The two descriptions of the demands of ethics in healthcare can be specified as follows. On the one hand, the reluctance (that is presumably to be observed) to forego clinical gains for a cost reduction would reveal a fundamental discontinuity among the choices we can make in healthcare compared to other domains. According to this stance, to adopt a health intervention would be an exception to other choices akin to that of buying a new house or other goods and services. This stance can be designated as of a *healthcare exceptionalism*. On the other hand, the opposite stance is based on the idea of a continuum and will accept cross-domain heuristics, such as balancing costs and outcomes, while accounting for domain-specific intrinsic characteristics explaining that some choices will be "tolerable" (Arrow 1963) if and only if some conditions are fulfilled, specifically in healthcare compared to other commodities without further specification. This stance can be designated as of a *healthcare continuism*.

☛ *Some respondents wondered about the morality of what they perceived as an equivalent to "sacrifice the few for the many". They also reported difficulties to accommodate the twin goals of privileging collective interests and of preserving a trust-based relationship among individuals (doctors and patients).*
☛ *Some other respondents held the view that patients cannot be offered the full range of treatments "whatever it costs [which] is an awful principle"; in that sense, they considered d-CEIs as a form of solidarity.*

2.2 – From stances to different practicable positions when making decisions in healthcare: ready to go West?

When exploring the place of d-CEIs in healthcare decision-making on the whole spectrum between disregarding it (on the rationale of a healthcare exceptionalism) and considering it (on the rationale of their cost-effectiveness), one may identify intermediate positions, depending on whether cost-effectiveness will be systematically or selectively disregarded or considered. Hence, four standard options for decision-makers can be identified, when considering healthcare alternatives in different situations:

- Systematic disregard: a decision-maker (1) who would dismiss cost considerations and only focus on improving health outcomes.
- Selective disregard: a decision-maker (2) who would consider costs only if health outcomes are improved.
- Selective consideration: a decision-maker (3) who would consider costs differently depending on whether health outcomes are improved or reduced
- Systematic consideration: a decision-maker (4) who would consider costs in a consistent way irrespective of whether health outcomes are improved or reduced.

☛ A decision-maker (1) could be illustrated by the following statement: "If healthcare is my priority, neither option is appealing".

☛ A decision-maker (2) could be illustrated by the following statement: "[the covid-19 crisis made me] less willing to accept [a health loss] because it has shown how important underlying health is".

☛ A decision-maker (3) could be illustrated by the following statement: "A small reversible change (which may not be experienced by all patients) is acceptable".

☛ A decision-maker (4) could be illustrated by a respondent who justified indistinctly his choices between the two interventions suggested by the "efficiency" criteria

In this exercise of differentiating possible heuristics (forms of reasoning) that a decision-maker can apply with respect with decrementally cost-effective interventions, it appears that these forms can reflect alternative axiological (value-laden) attitudes, but it is also possible to apply different heuristics in different contexts, reflecting a pre-defined typology of situations. On the one hand, a decision-maker would adopt one of these attitudes consistently and independently of the situations at hand, based on a description of ethics demands. Typically, the main ethics positionings involved in the discussion of the role of cost-effectiveness analysis in healthcare contrasts deontological or duty-based ethics (such as medical ethics) with teleological or end-based ethics (such as utilitarian or welfarist descriptions). On the other hand, a decision-maker might adopt different positions in different situations. Obviously, such variations would be highly problematic if they happened on a case-by-case basis, without any decision-rule.

Nevertheless, a differential attitude can be acceptable if taking into account other aspects than the cost-effectiveness based on identified criteria.

The debate on decremental cost-effectiveness evolves on the background of the tension between substantive ethical positionings, emphasizing on individual versus collective aspects and meanings of "improving health". Nonetheless, it is important to stress out that such a dualism is not necessary nor inescapable. By doing so, it allows to identify two practicable ways for incorporating decremental cost-effectiveness in the decision-making process without taking side for a substantive teleological approach, nor disqualifying legitimate deontological ethical concerns:

☛ "For patient that are in trouble because of their illness, we shouldn't even consider reducing costs".

☛" Health is the most important value. If somebody is ill, other activities/areas are significantly affected by this situation".

However, other values were opposed to these deontological arguments, insisting on the context of scarce resources and the need for solidarity and equity.

☛ *"Yes, decremental cost effective interventions may be accepted if they are useful for the overall population. With the COVID, we saw how a wide range of population can be affected and it fostered solidarity. Decrementally cost effective interventions are a form of solidarity (for other patients that will benefit from the money saved, that will be used for other treatments)"*

- When considering decrementally cost-effective interventions, deontological considerations can be reintroduced by topologizing conditions that need to be fulfilled before considering decrementally cost-effective alternatives. These conditions can hold on the severity of the disease (e.g., excluding severe conditions or end-of-life care), on the reversibility of the health loss, on the level of expected cost-savings (e.g., excluding interventions bringing no collective gains), etc.
- Situations might be identified (such as drug shortages, resource limitations, public health priorities, etc.) where the consideration of d-CEIs could allow the definition of priorities and maximization criteria on a fair basis, likewise the consideration of incremental cost-effectiveness ratios provides information on how to maximise health while preserving a fair allocation of healthcare expenses.

The first way designates the possibility to articulate decremental cost-effectiveness with structuring social and ethical values; the second way designates the possibility to coordinate different perspectives on d-CEIs without requiring from people involved in the decision-making to agree on a substantive ethical positioning. This is certainly a major characteristic of making decisions in a healthcare democracy, that *"we should not wish away the fact that we find ourselves living and acting alongside those with whom we do not share a view about justice* [or ethics]" (Waldron 1999).

Before going deeper in the ethics and philosophical discussion, it is important to highlight that, even if technical debates mainly oppose tenants of substantive ethical theories, a decision-maker can adopt a flexible attitude towards the question whether considering decrementally cost-effective interventions. One has the latitude, under this respect, to adopt one position or the other, namely to consider or to disregard decrementally cost-effective alternatives depending on the stakes of the decision to be made. One also has the possibility to agree on decremental cost-effectiveness as a decision-rule or as a valuable information to consider in complex situations, where colliding priorities or values cannot all be accommodated or where the alternative would be the absence of any decision-rule (Waldron 1999).

2.3 – Against a 'slippery slope' argument: into the West, but not too far

The four possible positions defined above (systematic disregard, selective disregard, selective consideration, systematic consideration) allow to better characterize the distinction between considering and adopting a decrementally cost-effective intervention. It may seem trivial to say that former does not imply latter. Decision-makers will in fact be more likely to "adopt" strategies in the South-West quadrant if they "consider" them, but the absence of an automatic relationship between the two terms involves that they can always reject a decrementally cost-effective strategy in the end. Decision-makers of the continuist stance, who will consider cost-effectiveness even when it is decremental (by difference with decision-maker (2)), will always come to reject some options despite their positioning in the South-West independently of deontological or value-based considerations as outlined earlier.

This is an important point to document to prevent a "slippery slope" argument. Such argument is either fallacious or deadly strong in ethics. It would consist in denying any ethical plausibility to the consideration of decremental cost-effectiveness based on the idea that, even if it might be highly useful or even acceptable in some instances, this would lead a decision-maker to accept any other quality-reducing intervention as soon as it would be cost-saving. This argument would contend that once a decision-maker would have come to accept a decrementally cost-effective strategy, he would then be led to accept any 'cheap and dirty' alternative at the expense of better, costlier comparators. To put it differently, to make the case that it can be ethically licit for decision-makers to take d-CEIs into consideration in healthcare, one must defeat the argument: 'once in South-West, everywhere in the South-West'.

The distinctive feature of decremental cost-effectiveness from an ethics perspective is the prospect, to a certain extent, to forego health outcomes for a cost reduction by considering – and maybe

adopting – a decrementally cost-effective strategy A versus an incrementally cost-effective strategy B. This prospect will be 0% in decision-makers (1) and (2) and it will not be certain (<100%) in decision-makers (3) and (4) as a direct consequence of the analytical framework of cost-effectiveness analysis, that is based on comparing between differential cost-effectiveness ratios of comparators, namely A and B in this example. The combination between costs and outcomes in A can take a meaning only with respect to cost-effective alternative B. Decision-makers (3) and (4) will be able to answer relevant questions such as "is cost-reduction in A enough to justify adoption?', 'is outcome-reduction too broad to justify non-adoption?", etc., relative only to the cost-outcome combination in B. The magnitude of costs and outcomes reduction in A cannot be addressed in absolute terms; its interpretation will be driven by the combination observed in strategy B. Decision-makers (3) and (4) will therefore not consider potentially decrementally cost-effective situations indistinctively. Before additional ethical conditions come into play, wherever the costs-outcomes combination in A will be inferior or equal to the one in B (the lines between A and the origin and B and the origin will be aligned), strategy A will represent a decrementally cost-effective alternative to strategy B. This strategy A will be worth consideration for both decision-maker (3) and (4). Conversely, both decision-makers (3) and (4) will reject strategy A as soon as it will present a worse costs-outcomes combination than B, namely when A will stand above a line passing through B and the origin. Decision-makers (3) and (4) will therefore go South-West, but in any case, not farther West than decision-maker (2) would go North-East. The farther in the West for decision-makers considering d-CEIs is when these interventions will show a differential cost-effectiveness ratio equal to the one of the incrementally cost-effective strategy. Finally, decision-makers (3) and (4) will possibly differ where A will present a better costs-outcomes combination than B, decision-maker (3) being prone to adopting both strategies A and B, and therefore applying different ratios in different quadrants, while decision-maker (4) would tend to reject strategy B as not being cost-effective.

To answer the 'slippery slope' argument: a decremental cost-effective intervention is so with regard to a higher costs-higher outcomes comparator; wherever clinical benefits can be brought to patients because an effective intervention exists, there is a limit a priori to the magnitude of health outcomes that can be foregone with respect with any cost-reduction that might be considered. A consistent decision-maker (3) or (4) would not adopt any possible intervention positioned in the South-West compared to the incrementally cost-effective alternatives.

2.4 – Is decremental cost-effectiveness akin to 'harming' patients, or is there any 'risk-ceiling'?

The interdependency between decrementally cost-effective strategies and the comparators located in the North-East quadrant may still raise important ethical concerns. A first concern is about missing a chance when opting for A against B; another concern is that the higher the cost-savings, the higher the acceptable level of losing effectiveness, letting decision-makers (3) and (4) deprived of any kind of "risk-ceiling". To be thoroughly addressed, these issues will need further research and discussions articulating careful analyses on the ethics and technicalities of decremental cost-effectiveness. Some key aspects deserve to be outlined because they will provide decision-makers with important landmarks in the debates to come.

☛ *"Health is an individual good, universal and collective, which makes difficult to deal only with economics or costs aspects"*

☛ *"The whole issue of savings is a big area for discussion. In our HTA committee the Finance Directors often say that savings identified in economic models are not realizable, so this is a concern ».*

☛ *"if disease severity is moderate or high, I choose to improve the quality of life"*

The first concern is about the risk of an incompatibility between decremental cost-effectiveness and the ethical principle that comes first in the lexical order in healthcare, namely *"first do no harm"* (*Primum non nocere*). This principle has been termed in contemporary bioethics as the "nonmaleficence" principle (Beauchamp and Childress 2001). The position in the South-West quadrant can be misleading under this respect and it is important to prevent any misreading of the ethical meaning one can give to this graphical representation of decrementally cost-effective situations. Differences in costs and differences in outcomes are reported on the *y*-axis (the vertical axis) and the *x*-axis (the horizontal axis), respectively, with neither costs nor outcomes being represented in absolute terms. Accordingly, the origin of the axes does not denotate any zero cost-zero outcome situation. One can therefore not interpret the origin as a minimal reference situation where one would not treat, at no cost; there is no possible realistic interpretation of the origin as corresponding to a possible situation that might be empirically observed. Such an interpretation might be possible *if and only if* costs and outcomes were reported in absolute terms and *if*, in this case, the origin was at the bottom left of the cost-effectiveness plane, figuring an hypothetical 'zero-cost, zero-benefit' situation. But if it was the case, in the above example of strategy A and strategy B, strategy A would stand in the same (and only) quadrant as strategy B and simply stand on the cost-effectiveness frontier with B, namely on the line connecting the interventions, "for which there are no other interventions that provide a better (or identical) health outcome at a lower cost" (HAS 2020). This is not what is meant when figuring four quadrants allowing to capture decrementally

cost-effective situations. It would be a mistake to overlook that the cost-effectiveness plane and the related quadrants are not realistic, but are logical constructs for analytical purposes. The origin of the cost-effectiveness plane does not have any ethical meaning or moral signification *per se*, since it does not reflect any reality that might be interpreted in phenomenological terms such as 'abandoning patients' or 'giving-up clinical care', and the like. Any reading of decrementally cost-effective strategies as "harming" patients would be flawed.

Such a misreading of the cost-effectiveness plane would double itself in a misreading of the "nonmaleficence" principle. An expectative attitude in medicine, "watchful waiting" when unsure about the therapeutic approach to adopt, is part of the diagnostic reasoning (Fagot-Largeault 2010) and involves active clinical care such as best supportive (or palliative) care. Such care already involves resource consumptions and brings benefits to patients; in addition, it can be dispensed separately or combined with active therapies. In any case, it does not come, when considering decrementally cost-effective alternatives to a costlier intervention, about depriving patients of clinical care. An epistemologically careful reading of the constructs of health economics is key for a sound ethical discussion and allows one to make a step further in the direction of alleviating the ethical difficulty of accepting to forego some clinical outcomes. The cost-effectiveness -plane and -frontier offer simplified views and analytics on the available evidence at the time of the decision-making. For instance, points A and B are figuring a costs-outcomes combination in strategies A and B. These combinations will vary in every patient, given differential response to treatment. The two points on the plane therefore shall themselves be read as surrounded by a confidence interval describing 95% of the joint distribution of costs and outcomes that one can expect to observe in real-life (Fenwick, O'Brien et al. 2004). This interval is itself the result of clinical and economic modelling and will be wider or tighter, depending on the quality of the clinical evidence that is available at the time of the decision-making. Let suppose that A is a well-known drug while B is entering the market based on a phase 2 non-randomized trial. A would have a tighter confidence interval than B. In specific situations, such as in a front-line treatment in a good-prognosis disease, it could make sense to go for the effective, well-tolerated, drug A – keeping alternative drug B in case of a relapse or of progressive disease. In addition, confidence intervals of A and of B may overlap and, especially in situations where only immature evidence about B is available, strategy B might extend on various quadrants of the cost-effectiveness plane. Accordingly, the representation of A and B centered on a mean point in the distribution will, as a rule, lead to overestimation of the gap between the two alternatives.

The main ethical issue with decremental cost-effectiveness could be about the question of setting a limit to the sacrifice one may accept in terms of outcomes-reduction. This issue of whether a 'risk-ceiling' might be defined has been only partially addressed in the above developments. Two cases remain especially problematic in this view, namely if B brought major clinical improvements at a very low cost or if A was extremely cost saving. In the first case, the question is that the line between B and the origin would be very flat, meaning that almost any technology in the South-West quadrant might present a decremental cost-effectiveness ratio standing below the line passing through B and the origin; in the second case, the question would be that the cost-savings in A could possibly compensate for high health losses without altering its costs-outcomes combination. These two cases will certainly deserve further ethical discussions and the present inquiry can propose three tentative landmarks that can help decision-makers:

The 'slippery slope' argument has not been addressed but respondents were more focused on the "acceptable risks" *and the possibility to assess these risks.*

☛ "It depends on actual situation in country, however I think if the risks (health loss) of this therapy will be low, the therapy may be considered."

☛ "I think the COVID-19 has reaffirmed the absolute priority of health and its inestimable value"

- In the case of B being extremely effective at an extremely low cost, the confidence interval as described above would overlap the North-East and the South-East quadrants (Fenwick, O'Brien et al. 2004); in this situation, a decision-maker would presumably have no reason to seek saving costs since the strategy B would be highly cost-effective or even dominant (cost-reducing, outcomes-increasing).
- In the case of A being extremely cost-reducing and standing on the line passing through B and the origin (maintaining a decrementally cost-effective combination between costs and outcomes despites a high outcome reduction), the solution is not as clear, but two lines of response can be identified. First, this can be a typical application of the difference between decision-maker (3) and (4): if accepting different cost-effectiveness combinations in the South-West and in the North-East quadrants, one can set limits to the level of outcomes reduction that can be acceptable in consideration of the costs saved; this amount defining explicit cost-effectiveness thresholds, at least in the South-West quadrant. Second, if adopting the position of decision-maker (4), namely that the cost-outcome combination shall be the same North and South, it might help to adopt a clause such as "the maximal combination in the South-West quadrant should be defined in consideration of the maximal combination (or willingness-to-pay) observed in the North-East quadrant".
- Another clause might be considered for further discussion, such as limiting the level of acceptable health losses in consideration with the health gains observed in the North-East

quadrant. In health conditions where clinical benefits are limited, such a clause would set a limit to what might be lost in consideration of a costs-reduction. In health conditions where different cost-effective technologies are available bringing incremental clinical gains, one might consider to define the "risk-ceiling" (the maximal health loss) in consideration with the benefits brought by the first technology on the cost-effectiveness frontier.

These tentative landmarks reveal the importance of deliberating beyond the observation of the cost-effectiveness plane. The two cases show how far a fair allocation of healthcare resources is from mechanical interpretations and applications. On the contrary, the reference to graphical representations as a decision rule can create an artificial perception of a collision between ethical and economic perspectives on decrementally cost-effective alternatives.

2.5 – Is decremental cost-effectiveness "wholly unethical" or is this uncertain?

The exceptionalist stance, especially as illustrated by decision-maker (1), is rooted in a strong assumption about a collision between ethics and economics, based on the premise of an incompatibility between healthcare decision-making and economic reasoning. As seen above, the move from the description of intrinsic characteristics of healthcare goods and services (even setting apart the question of the ability to reach an objective list of these characteristics) to the normative conclusion that "cost should not be a factor in medical care" (Loewy, 1980) involves a value-judgement backing the inference. Such value-judgement is not in itself problematic, but it is not necessary, either. To demonstrate this, and to defeat the axiological stance that costs are wholly unethical in healthcare, it is enough to show that at least another value judgement might lead to the reverse move, namely, to accept cost considerations in that domain.

The values underlying the position consisting in a 'systematic disregard' of cost considerations in healthcare collide with other ethical values worth promoting. Typically, decision-maker (2) would acknowledge the social benefits from privileging cost-effective strategies over alternatives bringing no extra clinical benefit for the additional money spent; in the above illustration, he would adopt strategy B and reject strategy C. This discussion allows one to pinpoint the existence of a reasonable disagreement on the value-judgements that are susceptible to underline various conceptions of decision-making in healthcare. Responding to Erich Loewy's argument, Alan Williams summarizes this by stating that, if some may consider that costs should not be considered, others may equally plausibly hold that "they are mistaken in this belief, because it cannot be ethical to ignore the adverse consequences upon others of the decisions you make, which is what 'costs' represent" (Williams 1992). As Alan Williams is himself an economist, this is an illustration of the opposition

between the two ethical stances, exceptionalist and continuist, identified in the first part of this inquiry. But the point here is that decision-maker (2) could accept Williams' contention, for instance when waiving to adopt treatment C. The stance that cost-effectiveness might be "unethical *per se*" therefore rests on a value-judgement that is not necessary and that overlooks other important ethical values in healthcare pertaining to the collective implications of the decisions made. Under this respect, the consideration of the consequences that the decisions made can have on health care goods and services (such as on their accessibility, distribution, quality, etc.), in a collective perspective, needs consideration, as other ethical values in the perspective of the needs and due respect of the individual patient do. The tenants of an exceptionalist stance who would systematically ignore costs dimensions would in fact adopt a positioning that is not neutral, putting the cursor on some ethical principles at the expense of others and this stance is axiological (or moral) and, in fact, open to ethical discussions.

Different positions are therefore plausible as far as they are rooted in, and promote, different ethical values and principles. Exceptionalists will put emphasis on the therapeutic alliance and trust relationship between individuals, namely patients and prescribers; Continuists will do so on collective consequences and fair allocation of healthcare resources. Two ethics, individual and "egalitarian ethics" (Williams, 1992) can be contrasted in this view. While conceptual distinctions can be sharp, different values can be accommodated in practice. Decision-maker (2) tends to strike an equilibrium by considering costs dimensions when health outcomes are equal. Other equilibriums might be considered: decision-maker (1) will consider that augmenting overall resources allocated to healthcare will resolve the conflict of values. As shown in sections 2 and 4, decision-makers (3) and (4) can apply their heuristics conditionally, for instance, to set 'risk-ceilings' or to consider severity or other contextual aspects. However, the response 'it can be accommodated in practice' or, put differently, 'this is matter of policy', would beg the question whether decremental cost-effectiveness is, or is not, unethical.

☛ According to a decision-maker (2): *"The best option so far is huge savings, very small impact on health, only reverting back takes some time, but patients can wait, since the health loss is very small"*
☛ *According to a decision-maker (1): "I would prefer to just increase the health care budget and not make any concessions…"*

Decision-maker (1) and (2) would agree on this unconditionally. This contention of the exceptionalist stance is based on the view that cost-effectiveness analysis carries utilitarian axiological views; if one rejects these views, one would therefore be right to disregard the methods. Under this respect, the divide between the two ethical stances holds on different views about the epistemological status of cost-effectiveness analysis. This brings important clarifications on the origin of the contention that

'cost-effectiveness (moreover decremental cost-effectiveness) is unethical in healthcare'. It also corroborates the identification of reasonable disagreements and, therefore, that this contention is neither necessary, nor certain. In the literature, the core problem in the debate between opponents and proponents of the relevance of cost-effectiveness analysis in healthcare, is the problem of aggregating at the collective level, in a ratio, outcomes as well as consequences of discrete healthcare interventions. This is exactly what Alan Williams addresses, when he tells the reader, basically, that costs are not a money issue but a measuring tool for economists to value collective consequences; conversely, critics of cost-effectiveness analysis in healthcare focus on the "utilitarian maximization" behind economic methods to value health outcomes (Brock 2004). For harshest critics, health economics ought to be ethically disqualified in healthcare decision-making for it is held to encompass a supposedly biased utilitarian point of view: the exceptionalist view and medical ethics would entail "a preference for identifiable over statistical lives" (McKie and Richardson 2003); the continuist and economical view, the opposite.

One possible response consists in highlighting that cost-effectiveness analysis is, in fact, not only compatible with a utilitarian approach but also with many alternative theories of social justice when it comes to healthcare resource allocation. One may cite works by John Rawls (equity), Amartya Sen (capabilities), Ronald Dworkin (luck) or, in Europe, by Philip Van Parijs, Marc Fleurbaey, and others (Thébaut and Wittwer 2017). It is, therefore, inaccurate to equate cost-effectiveness analysis and sheer utilitarianism. The variety of plausible ethical theories behind the continuist stance, reveals the epistemological underpinnings of the divide about cost-effectiveness analysis in healthcare. From an exceptionalist point of view, economic theory entails utilitarian values and principles; this view rests on an idealist understanding of health economics, emphasising on the framing effect of underlying theories in the process of generating evidence and scientific knowledge. In this view, the information brought by health economics is supposedly fraught with theories and values and therefore irrelevant to healthcare decision-making or, at least, should be taken with caution because of the ethical issues "embedded in" health economics analytical tools (Pinkerton, Johnson-Masotti et al. 2002). Another understanding of the methods and measuring tools of health economics would rather insist on a pragmatist or instrumentalist epistemological reading based on the presumption of an independence between theories and analytic tools (Nadeau

In the DCE, the participants pointed out this need to produce and to share information based on cost-effectiveness analysis. They insisted on the security they provide and on the key role these information can play on the public acceptability and awareness :

☛ *"In order to make a significant cost-saving for the rest of the population, I would try to explain and communicate around the benefit for others"*

☛ *"Is a QALY a QALY? It would be great to develop this as a TV game to help the population simply to think about all this (and give opinion)"*

1999); according to this view, cost-effectiveness analysis can be relevant in healthcare as far as it will provide adequate evidence and useful information to decision-making.

Being aware of the caveats of the cost-effectiveness analysis in healthcare, that are extensively addressed in the economic and ethics literature on social justice and resource allocation in healthcare, a decision-maker can adopt a pragmatic approach on the information provided by health economics tools when considering whether cost-saving interventions can be held as decrementally cost-effective.

2.6 - "Obfuscating" or "illuminating": middle ways to sustainable healthcare?

Idealist critics allow for the relevant challenging of economic quantification tools. Two main lines of argument are raised by the opponents to economic quantification in healthcare. Both arguments can possibly undermine the pragmatist criterion of adequate, useful analytics. The first argument is that cost-effectiveness analysis fails to capture, through its quantifications, the meaningful consequences that are relevant for a sound decision-making in healthcare. In 1980, the Office of Technology Assessment made a report to the Congress of the United State where the Office identified different views and related scenarios about the integration of cost-effectiveness analysis in the decision-making process in healthcare (OTA 1981). These views ranged between two "extremes", namely from the view that cost-effectiveness analysis is "obfuscating the pertinent issues in a decision process" to the opposite view that it is "illuminating and synthetizing these issues so well that the technique can be used to make decisions" (p. 5). A tenant of the exceptionalist stance would hold here that cost-effectiveness ratios actually fail to capture the relevant ethical dimensions to be incorporated in the process of making decisions in healthcare; accordingly, cost-outcomes combination might be considered in simple cases as when a strategy C is simply costlier while equally effective than an alternative strategy B, but cost-effectiveness should not be considered wherever the stakes of decisions are trickier. The second argument developed in the literature relates to an alleged "scepticism" of decision-makers about the results of cost-effectiveness analysis; for the focus on incremental cost-effective situations would in fact lead to "the practical consequence of […] an increase in health care expenditures" (Birch and Gafni 2006).

A way for health economics to respond to these critics consists of conducting further refinements on the quantification techniques used. For instance, authors rightly point out the difficulty for standard health outcome valuation techniques to account for the health needs of individuals with disabilities (Brock 2009); this case has long been a source of reflection and improvement

☛ *"[the covid-19 crisis made me realize the need] to be careful with short term health savings which can have a long term cost"*

of cost-effectiveness measurement tools (Ubel, Nord et al. 2000), (Rutstein, Price et al. 2017). In this sense, legitimate questioning about possible biases introduced in the quantification techniques by underlying theoretical orientations represents a potential for enriching health economics methods. The difference introduced by considering decrementally cost-effective strategies might be exemplified as follows. Cost-effectiveness analysis focuses on measuring direct consequences of health care on health and disregards indirect consequences such as collective benefits, for instance; this methodological standard receives an ethical justification on the principle "to give equal moral concern and weight to each person's health care needs" (Brock 2004). Although well-established when dealing with cost-increasing health interventions, this standard might have to be reversed when considering cost-reducing ones: in this case, to account for negative externalities may gain relevance, such as for instance "environmental externality" if promoting cheaper antibiotics was found to contribute to antibiotic resistance (Munthe, Fumagalli et al. 2021). Conditional to further research and ethics discussions, if such a methodological change proved to offer promising prospects to health economics to improve its analytical tools, this would show how taking idealist critics seriously can help to expand the instruments of health economics and to improve the value of the information provided to decision-makers.

Conversely, to reject decremental cost-effectiveness as unethical by overlooking such epistemological debates would lead to unfortunate practical consequences in a social environment where sustainability issues are gaining outreach in healthcare. One may reflect by analogy to another "collectivity-oriented" domain, namely clinical research, here. In the 1970s, an ethical debate of the same form took place on the question whether it ought to be expected from minors – who cannot provide explicit consent – to be willing, "because they are social human beings", to take part in experiments. The debate opposed tenants of a research exceptionalism on the one hand, and tenants of a continuistic view on sociality, on the other hand. Ethical justifications of pediatric research are now well clarified and a central continuist argument is that it is reasonable to expect of children to participate for they may come to value it later as a meaningful contribution to a social good (Wendler 2010). This does not mean that one may stop reflecting on the specifics of pediatric research from an ethics perspective, but the debate noticeably evolved from its origination in a frontal opposition between those considering children participation and those rejecting it as wholly unethical. The social environment at that time had already acknowledged the need for pediatric research to generate useful evidence, adequate to pediatric conditions, and both sides could agree that, without research,

☛ Respondents highlighted the social implications of a decrementally cost-effectiveness strategy : "half of the problem is missing in my view: what could be gained from cost-savings and how health gains and health losses would be distributed in the population"

children would be "the ultimate sufferers" (McCormick 1979). Interestingly, the exceptionalist stance took the perspective of decision-makers and, while holding pediatric research as unethical, contended that (Ramsey 1976): "Some sorts of human experimentation should, in this alternative, be acknowledged to be 'borderline situations' in which moral agents are under the necessity of doing wrong for the sake of the public good. Either way they do wrong. It is immoral not to do the research. It is also immoral to use children who cannot themselves consent and who ought not to be presumed to consent to research unrelated to their treatment. On this supposition research medicine, like politics, is a realm in which men have to 'sin bravely.' The researcher you can trust, the statesman you can trust, however, is the man who does not deny the moral force of the imperative he violates." Decision-maker (1) and decision-maker (2) would not view decremental cost-effectiveness as a "necessity […] for the sake of public good" and, conversely, decision-maker (3) and decision- maker (4) may cast doubt whether scarcity in healthcare might stand as a "borderline situation". However, this example suggests that the debate around decremental cost-effectiveness may evolve; rejecting it by adopting a disregarding attitude would actually leave decision-makers facing cost-containment or sustainability issues in healthcare without any guidance, except to "sin bravely" which means to apply double-standards when making decisions without transparency on the heuristics applied, rejecting decremental cost-effectiveness but practicing cost containment if needed.

2.7 – Decremental cost-effectiveness as an ethically licit route to consider.

At this stage, the main outputs are the following:

- To disregard decrementally cost-effective alternatives systematically is not necessary in healthcare; other ethical stances can be construed backing on equally relevant principles. Therefore, it cannot be held as a 'neutral' choice and actually faces serious ethical difficulties.

- Although it might at first sight seem the most plausible, to consider cost-effectiveness information only in incremental situations while disregarding decrementally cost-effective alternatives is itself ethically problematic and leaves decision-maker deprived of guidance when coming to tackling with the sustainability of healthcare systems.
- To produce information on cost-effectiveness including about decrementally cost-effective strategies allows to expend the attention to all alternatives for which there is no "better (or identical) health outcome at a lower cost". It might provide one response to the difficulties of cost-effectiveness analysis to contain the growth of healthcare expenditures.

☛ Some respondents put a specific light on the need to consider social factors such as "the social condition of people", "the health inequalities in the population", or "the knowledge about resources reallocation". They also pointed out the possible role the covid-19 played in order to consider these factors : " I think that the Covid-19 crisis has improved the political and societal acceptability of discussions on the trade-off between mortality, quality of life, freedom and economic and social conditions"

To summarize, to hold healthcare as an exception to economic evaluation is presenting important ethical limitations, whereas considering decrementally cost-effective situations can provide, along with the information of incrementally cost- effective alternatives, useful and relevant information in the decision-making process, under the condition of encouraging methodological research and ethics discussions. If it were enough, for the purpose of the present inquiry, to demonstrate that decrementally cost-effectiveness is not an ethically prohibited direction for decision-makers, it remains to show that it is not a dead-end either, by providing in the toolbox expected by WP11, a conceptual background for an ethically plausible approach to considering – and possibly adopting – d-CEIs in healthcare along with a demonstration that it can be practicable in European healthcare systems.

To allow decision-makers to consider all options, including decrementally cost-effective ones, still leaves room to find arrangements suitable to various institutional environments. The inclusion of alternatives showing a decremental cost-effectiveness ratio in resource allocation decisions can take different forms, ranging from considering this information to using it as a criterion for making decisions, and intermediate forms can be adopted such as including other criterions in the decision. In addition, to include decrementally cost-effective strategies in healthcare decision-making can be accommodated without modifying existing practices such as the place of cost-effectiveness in reimbursement decisions or in market approval workflows, while offering decision-makers additional information, and leverage, in price negotiations.

Two final observations can be made to complete this overview on the plausibility of considering decremental cost-effectiveness in healthcare. A positive effect on the public debate and a procedural requirement are highlighted in the literature on the ethics of cost-effectiveness in healthcare; both need to be included in the consideration of decremental cost-effectiveness.

> ☛ *"The opacity of these decision-making mechanisms leads me to wonder how to ensure that the savings made by less effective treatment choices are really redirected to other health or educational fields, for example?"*
>
> ☛ *"the general case seems to more related to patients across disease areas than same patients. Therefore much more information would be needed regarding social choices regarding trade-off across disease areas (rare vs. non-rare, pediatric vs adult, ..)"*
>
> ☛ *"[the covid-19 crisis allowed an] acuter perception of resources reallocation" or "the scarcity of resources have more clearly entered the public debate"*

On the one hand, the information produced by cost-effectiveness analysis, along with complementary information on other aspects, is useful in the sense that it can have a pragmatic positive effect on the transparency of the decisions made: it "exposes […] hidden assumptions, and requires explicit judgements to be made" (Williams 1992). One may read this argument on an inferentialist or epistemic background according to which producing additional information (compared to disregarding the information about cost-effectiveness) augments the number of "reasons" to be articulated in the public debate understood as "a game of giving and asking for reasons" (Brandom 2001). In this view, to consider decrementally cost-effective strategies can be seen as bringing additional value in this game. While incremental cost-effectiveness analysis invites reflection in terms of "opportunity costs" and collective willingness to pay for providing health outcomes, but often with limited demand for characterizing it precisely, the added value of considering decrementally cost-effective strategies might be to strengthen the quest for making explicit the identification and quantification of the collective benefits expected to be gained by foregoing corresponding health outcomes or, conversely, to be sacrificed if the final decision is to not adopt the decrementally cost-effective option but to keep on opting for incrementally cost-effective alternatives.

On the second hand, such a dialogue, such a quest for making underlying inferences and balances explicit and debatable, needs to be constrained by procedural requirements, such as transparency and participation. This is where making evidence-based decisions in healthcare, in the light of available knowledge and information (ultimately critically considered in the light of vivid methodological developments and ethics discussions), connects with the broader concept of health democracy. This is a very important argument developed in the literature, both in normative and pragmatic directions. Normatively, authors highlight the requirement for economics models (as for

any other source of evidence) to be transparent, to make it possible to understand theoretical and normative underpinnings as well as to identify articulations with other information of another nature, such as patient or public preferences, disease experience, and the like (Schlander 2008). Pragmatically, models have been developed and operationalized, building on broader philosophy of language and communication ethics, in order to provide decision-makers with efficient procedures to implement active participation and democratic deliberation in healthcare assessment and decision-making practices (Daniels, Porteny et al. 2015), (Byskov, Maluka et al. 2017).

This is where ethical concepts and models are turning to implementation issues, making the present inquiry complementary to the corresponding part in the toolbox expected by WP11.

☛ "How much more health can be created by using the cost-savings in implementing d-CE matters and can make it easier for patients to understand and/or accept a d-CE change from usual care."

Some respondents emphasized the need to keep a balanced dialogue with the patient targeted, based on understandable information.

☛ "I feel uncomfortable in forcing people to take a treatment with health loss if they cannot go back to the standard treatment. But I would be ready to let the doctor offer it to their patient on a voluntary basis."

☛ "[the attribute I would consider in order to adopt a decrementally cost-effective intervention would be] the patient's preferences" or "[the patient's] risk aversion or willingness to suffer any health loss" or "the opinion of the population consulted beforehand"

2.8 - Towards a contribution of ethics to a toolbox: building a roadmap into decremental cost-effectiveness.

To help decision-makers navigate from consideration to adoption of d-CEIs, the above ethics inquiry can be completed by:

- Defining a conceptual background that provides clear landmarks for an ethically plausible approach to d-CEIs in healthcare.
- Building a roadmap in order to demonstrate the practicability of d-CEIs in healthcare by listing questions whose responses can accompany a decision-maker from considering to adopting a decrementally cost-effective intervention.

The following ethical guidance builds on two conceptual continuums who are germane to the concept of a democracy. The current concept of democracy builds on two legacies: of the period of the Enlightenment in the XVIIIth century and of the Greek and Latin Antiquity through the lenses of the XIXth century. Consequently, two meanings of a "society" tend to coexist in contemporary forms of democracy, as a civil bound (*Gesellschaft*) and as a community (*Gemeinschaft*). Contemporary democracies are therefore building on a dual-nature social bond, based, on the one side, on a "rational will" (to live *with*) and, on the other side, on a "natural will" (to live *together*). The identification of this intrinsic difference can be traced back in the political philosophy of Jean-

Jacques Rousseau (Genette, Bénichou et al. 1984)[21] and declined in two relevant conceptual continuums:

- Between the individual as a citizen and the individual as a single person, which raises questions about the "participation", in its direct, indirect, and mixed forms.
- Between the general knowledge and personal experiences, which raises questions about the "recognition" of individual needs in the appreciation and sharing of common goods.

Every democratic setting, every institutional design in a democracy, can be seen as varying positionings along these continuums. As an element in broader democratic institutions, healthcare decision-making, in the form of health technology assessment, takes place in this broader conceptual landscape and related institutional positionings.

When coming about considering and adopting decrementally cost-effective interventions, an ethical and political guidance will be useful if it can help positing decision-making along these continuums of "participation" and "recognition" by identifying practices that can be compatible with the demands of democracy in terms of social acceptability (legitimate decision-making) and in terms of knowledge (evidence-based decision-making).

2.8.1 - A conceptual framework for democratic deliberation on d-CEIs.

The consideration of d-CEIs mobilizes sophisticated health economics techniques and can develop on the background of complex ethics issues and discussions. This can be said of the technical domains of health technology assessment (clinical effectiveness analysis and cost-effectiveness analysis); it is not specific to d-CEIs and the need for expanding HTA to include broader social aspects is long-established.

On the specific case of decrementally cost-effective interventions, there is a need for clarifying how additional prospects and margins for reallocating healthcare resources can be compatible with the overall democratic environment, given that the mechanism to that end is to accept to forego, to a certain extent, some health outcomes in specific populations.

A simple conceptual framework, based on three key concepts, can be proposed to clarify how this objective and its mechanism can be practiced in health democracies. These three concepts allow light to be shed on the most important ethical and political aspects when considering d-CEIs and offer three landmarks that will prove useful in the next section, when structuring a roadmap for

[21] See the chapters by Léo Strauss and by Victor Goldschmidt.

decision-makers when balancing whether to adopt or to reject a decrementally cost-effective intervention.

Proportionality

The proportionality principle is a first concept that can help paving the way how one can reflect on decrementally cost-effective interventions. It is a common reference in Europe and can be operationalized in various domains of health technology assessments, such as when documenting the legal, ethical or cost-effectiveness aspects of alternative comparators.

Proportionality is a fundamental legal and political principle in the European construct. It is rooted in the legal enforcement of civil and individual liberties in the 1950 European Convention on Human Rights. Apart from absolute rights, as for example the right to life (art. 2) or the prohibition of discrimination (art. 14), State or public action can set limits to the exercise of the other rights. By doing so, a State must have an aim to foster a legitimate collective interest and "proportionate" its interference in the corresponding rights of individuals (as for instance the right to respect for private and family life, art. 8). In this balancing exercise, a "national margin of appreciation" is acknowledged to the State. This is the principle, in European law of a subsidiarity of supra-national institutions with respect to national authorities, acknowledging to national decision-makers a privilege when deciding on the appropriate actions to take, typically in the organisation of their healthcare system.

This principle can be viewed as a latitude and as a responsibility for the States. Any public action, indeed, can have to be justified in the light of this principle. It comprises three tests through which a public action, and the related interference in individual rights, can be deemed proportionate (legitimate) or disproportionate (illegitimate). The first test consists in justifying the adequation (*Geeignetheit*) with the collective end pursued: the interference must at least represent an appropriate mean to promote the collective interest it is aimed at. The second test requires the demonstration that the interference was necessary (*Erforderlichkeit*), namely that the end was unattainable using a mean that would have been less intrusive in the individual interests. The third test is a dynamic requirement meaning that the State must show that the interference is always strictly proportionate (*Verhältnismässigkeit im engeren Sinne*) as the aim it is realizing, as the environment of the public action is changing accordingly; it requires that the interference stops as soon as the aim is attained or to temper it down whenever possible.

These tests can be used *ex post*, to "produce reasons" (Brandom 2001) backing an interference, or prospectively, as a heuristic tool to ascertain the righteousness of an action planned. The two uses

are common in ethics in the form of the theory of the "double effect". This theory originates in Thomas Aquinas' philosophy and calls for a strict analysis of the moral quality of an action when judging its consequences. In contemporary bioethics, this theory calls for differentiating, of two actions with the same consequences (maximising benefits or minimising harms), the one that can be deemed ethical and the one that is unethical (Foot 1967). Basically, in health, it can be ethically licit for an action aiming at a collective good (outcome maximization) to have negative consequences on some individuals (outcome reduction) if and only if the harm to these individuals is an indirect (unavoidable) consequence and was not aimed at them[22].

Dialogue

Such tests can only lead to tentative and debatable conclusions. In law, the proportionality of public actions is often disputed, as for example the rich case-law before the European Court of Human Rights concerning State interferences in health or in the access to healthcare[23]. Conclusions on the ethical liceity of foregoing some health outcomes will also be exposed to debate and discussion. From a philosophical point of view, disputes and discussions are part of a rational game of "giving and asking for reasons" (Brandom 2001); disagreement is natural to a rational deliberation. The concept of "dialogue" is put forward by philosophers and legal theorists, both to describe the logical structure of valid inferences (Heinzmann 1992) and the nature of legal rights which can be defined only through "a collective learning process" (Van Hoecke 2002).

In this view, the definition of ethical boundaries to d-CEIs will require the instauration of such a dialogue or "rational political conversation" (Ingram 1994), that can be cooperative (based on consensus-seeking and agreement) or eristic (based on debate and dissension). This "conversation" needs to be established on the articulation, in the consideration and adoption of decrementally cost-effective interventions, between limitations and interferences in the rights of individuals and the collective interests made attainable by the reallocation of cost-savings. There is currently no certainty, guidance, or landmark about what could be held legal, ethical or acceptable in this respect. For this reason, "political conversations" on the topic must be encouraged both in the rational, collaborative environment of health technology assessment agencies and in the broader public debate.

[22] To take Philipa Foot's example, it would never be ethical to kill a man to transplant his organs to five patients.

[23] https://www.echr.coe.int/documents/fs_health_eng.pdf

Although it will reveal conflicts and disagreements, this will trigger "a process of deliberation that may be represented as a social discourse" (Ingram 1994), leading proponents and opponents to decremental cost-effectiveness to make explicit their claims about the realm and boundaries of what can be held ethical or unethical in this matter. This is an exercise of health democracy and it offers a strong basis for the implementation of effective participation pathways and for encouraging transparency, allowing stakeholders to get actively involved in this process, especially patients and prescribers whose care and professional experience will be altered by the adoption of a decrementally cost-effective intervention. One important responsibility of those who will consider and dialogue on the adoption of d-CEIs will be to organise this participation but also to accept the emergence of "earnest disputes" without seeking "a universal commensurating discourse" (Willard 1996). This way, different types of knowledge, the "evidence-based" and the "experiential", can be articulated. Active means to warrant participation of the individuals, through efficient stakeholder involvement, can contribute "to 'enlarge the possibility of intelligible discourse' by lowering the price of collaboration" (Willard 1996).

Temperance

To consider d-CEIs is intrinsically linked with the idea that, in some instances, a certain level of effectiveness might be *enough*, allowing margins of action *elsewhere*. The notion of decremental cost-effectiveness invites one to think both in terms of "not *too* much" when demanding for efficacy, but also in terms of "not *too* far" when engaging in cost-reduction. Beyond a mere cost-containment mechanism, the concept of "temperance" in its various philosophical meanings elicits the intrinsic conceptual link between the reflection on d-CEIs and fundamental concepts for the ethics reflection of fairness, rationality, and sociality.

The concept of temperance, or moderation, designates ethical virtues of an individual or of a collective. It is tied to the concepts of justice or fairness and takes an individual and a social meaning from the Aristotelian descriptions in the *Nicomachean Ethics* (V, on Justice). For an individual, an unjust man "does not always take more than his share [of good things]; he sometimes takes less of those things which are bad". In the view of a society, "what is fair or equal is a mean between more or too much and less or too little"; it would be unjust to treat equals unevenly or to treat non-equals evenly. On this basis, a temperate decision-maker considering a decrementally cost-effective intervention will reject it if it would imply giving the patients who will be concerned less than their share of benefits or more than their share of risks. Beyond this individual risk-benefit balance, a temperate decision-maker would also reject the intervention if it would imply giving to those who will benefit of the reallocation more than their share; a temperate decision-maker would not

sacrifice the worse-off even if it would maximise benefits at the collective level. Conversely, an individual rejecting a decrementally cost-effective intervention that would satisfy the above criteria might, like the "unjust man", take less than his share of the necessary efforts for a legitimate collective gain.

In the philosophical tradition, the concept of temperance evolved beyond this ethical meaning. Following three examples will provide an insight on the breadth of the concept and it can help articulate key issues when considering decrementally cost-effective interventions:

- Aristotle's philosophy delineates a method to know what can be predicated "just" or "unjust". This meaning of temperance as a method evolved over the medieval philosophy to designate a cognitive capacity ("charity") to understand the reasoning held by an another individual or to reason with him, as in the *Metalogicon* of John of Salisbury.
- Baron d'Holbach, in the XVIIIth century, exemplifies a link between an individual concept of temperance and a political concept of social contract through the notion of reciprocal welfare, which implies for the individual to surrender a portion of individual goods for entering the civil bound: "Secure for me advantages great enough to persuade me to give up to you a part of those which I possess".
- In the XIXth and XXth centuries, the concept of temperance gains a new ethical meaning as a mean to the recognition (Fichte, Anerkennung) or the self-esteem (Goethe, Entsagung). For the other to emerge as a self-conscious individual, I must accept to relinquish parcels of powers. In the contemporary ethics, Axel Honneth coins together the quest for "emancipation" and the "destruction of asymmetries and social inequalities"; thus, the need for the better-off to accept to forego some advantages.

These three examples in the history of philosophy highlight the intrinsic link that can exist between the sociality and the capacity for an individual to identify and to renounce – but for a fair and proportionate part! – to a part of his share of benefits.

2.8.2 A roadmap to making decisions on d-CEIs by answering key questions.

Guided on the three concepts of proportionality, dialogue and temperance, the consideration of d-CEIs appears practicable in health democracies and might even contribute to intensifying "rational conversations" among the stakeholders on the definition of healthcare priorities and the most efficient ways to their realization, taking social justice and fairness considerations into account.

The different steps towards considering a decrementally cost-effective intervention and deciding whether to adopt it can be mapped as in the figure below and described as follows.

If a decrementally cost-effective intervention is adopted, individuals can be either impacted in their personal or professional life or enter in the process directly by playing a public role in the dialogue (such as an expert, a policy-maker, a civil-servant, a stakeholder, etc.). The individuals who can be impacted are typically the patients and the prescribers. The prospect of a d-CEI being adopted raises two different issues, respectively. On the patients' side, the general question concerns the articulation, when having a disease and healthcare needs, between rightfully expecting solidarity and "sharing in sociality" (McCormick 1976). Research participation is but one illustration how patients can participate actively in common good and the social fabric; accepting a decrementally cost-effective intervention might be another one of these. On the prescribers' side, the general question is about the compatibility between accepting to forego some clinical efficacy and the professional role of medical doctors as agents of the interest of their patients. Doctors' collective obligations towards the society, as well as many instances where appropriate prescription can involve watchful waiting or therapeutic de-escalation, can provide enough room to challenge the immediate idea that a doctor's agency would command them to systematically do the most that is clinically possible. Those potentially impacted by the adoption of a decrementally cost-effective intervention can therefore answer questions such as 'how they would be impacted?', 'how negative would it be?', 'how might this sacrifice be useful to others?'. On this experiential basis, they can decide either to challenge the adoption of the decrementally cost-effective intervention in the broader public debate, or to contribute this experiential knowledge to the process, leading to further consideration of the adoption of the decrementally cost-effective intervention, or both. The second and third modalities are key, allowing patients and prescribers to participate in the dialogue when it is considered, at the society level, whether a decrementally cost-effective intervention should be adopted.

In Lindström and Waldau (2008), authors describe how patient organisations can participate in the deliberation on prioritizing access to scarce healthcare resources and concurrently keep advocating in the public debate for rising budgets allocated to the healthcare goods and services at hand (in vitro fertilization in this instance). This important point has two ramifications: First, "participation" improves the evaluation and deliberation process on the adoption of decrementally cost-effective interventions, providing valuable information and maximizing social acceptability; Second, the conditions for a meaningful participation should determine the process underlying the evaluation of, and deliberation on, decrementally cost-effective interventions. Norman Daniels has been proposing a general model for a participative deliberation since the 2000s (Daniels 2000) and this model has been implemented in various HTA settings since then; the process values underlying this model ("accountability for reasonableness" or A4R) can provide useful references when considering

foregoing some health outcomes, namely: transparency or publicity (of the reasons for the adoption of the decrementally cost-effective intervention), relevance (of these reasons), revisability (in the light of new evidence), and enforcement (guarantees on the former).

Provided such process-values are enforced, the individuals potentially impacted by the adoption of the d-CEIs may (if they wish to) participate in the deliberation. The other participants can include, depending on the institutional settings, the traditional actors in health technology assessments such as experts, policymakers, user representatives, pharma, etc. The issue at this stage involves a question pertaining to the definition of the social contract in healthcare, namely whether the decrementally cost-effective intervention under consideration might constitute a legitimate interference in the freedom of choice of individuals for the sake of a collective interest. The deliberation will have to answer this broad question by responding to four general questions:

1. Why would the adoption of the decrementally cost-effective intervention be "adequate" to the end that is pursued? Under this question, the policy objective ('the aim') for which a cost-saving will be necessary can be elicited, such as improving population health, the sustainability of the healthcare system, the prioritization of health needs of vulnerable populations (see the appendix on "proportionate universalism"), the prioritization of access to scarce resources, etc.
2. Why would the adoption of the decrementally cost-effective intervention be a "necessity", namely the minimal interference in individual interests for an optimal realization of the collective benefit that is sought? This question can be informed by reviewing the available evidence on central characteristics of the decrementally cost-effective intervention, such as the reversibility of the health loss, or the uncertainty about the expected cost-savings. By doing so, decision-maker can evaluate if the risk of harming patient is minimized and if the prospects of cost-savings are realistic enough to warrant that the collective end is attainable.
3. Will the adoption of the decrementally cost-effective intervention permit a fair and non-discriminatory handling of the patients receiving it? This question can be responded *ex ante* and in particular situations. *Ex ante*, ethical tests such as "pairwise comparisons" can help secure an acceptable level of the sacrifice for the individuals. This test consists in checking "how we treat individual persons, one person at a time" allowing the prevention of undue

aggregations at the collective level at the expense of worse-off individuals[24] (Kamm 2015). Explicit principles for allowing access to incrementally cost-effective alternatives in case of a health loss deemed unacceptable by the patient, relapse or progression (*staged care*) could allow the adaptation of the decrementally cost-effective intervention to real-life situations and individual variations.

4. How can the adoption of the decrementally cost-effective intervention remain strictly proportionate to the aim? This fourth condition can for instance be informed by collecting additional real-world evidence allowing for the monitoring of variations in real-life of the cost-effectiveness combination of the decrementally cost-effective intervention and of its incrementally cost-effective comparator(s). Should this reveal an alteration of the differential at the expense of the decrementally cost-effective intervention, this might be a clear indication for a switch to usual care for all patients. Another way to satisfy the fourth condition consists of keeping active price negotiations on the costlier alternatives to reduce the price differential, allowing an improvement in access to the higher outcomes' alternative for all.

The following figure provides a tentative roadmap to a practice of considering d-CEIs in health technology assessment that could be ethically justified, and acceptable in health democracy settings. Following such a roadmap, decision-makers (including stakeholders) can be involved in participatory, evidence-based, and careful deliberations, up to responding to key questions before deciding whether to adopt a dCEI. This can lead to sounder decisions on cost-saving strategies but can also contribute to nurturing the public debate with explicit rationales on the checks and balances guiding healthcare public decision-making.

The list of key questions will certainly remain quite stable overtime, since it is based on standard proportionality tests, and thus on generic conditions to public action in democracies when it comes to interfering in individual rights for collective purposes. Future research, ethics discussions and experience-sharing will allow the specification and completion of this roadmap.

[24] To apply Kamm's example to the decrementally cost-effective intervention context, let say the decrementally cost-effective intervention would impact a few severely ill patients and the cost-savings would allow to treat numerous people suffering of a headache. Although the decrementally cost-effective intervention envisaged may maximise utility at the population level, it would fail the "pairwise comparison" test since nobody would agree *ex ante* that it could be reasonable to forego clinical outcomes in a severely ill to relieve a headache.

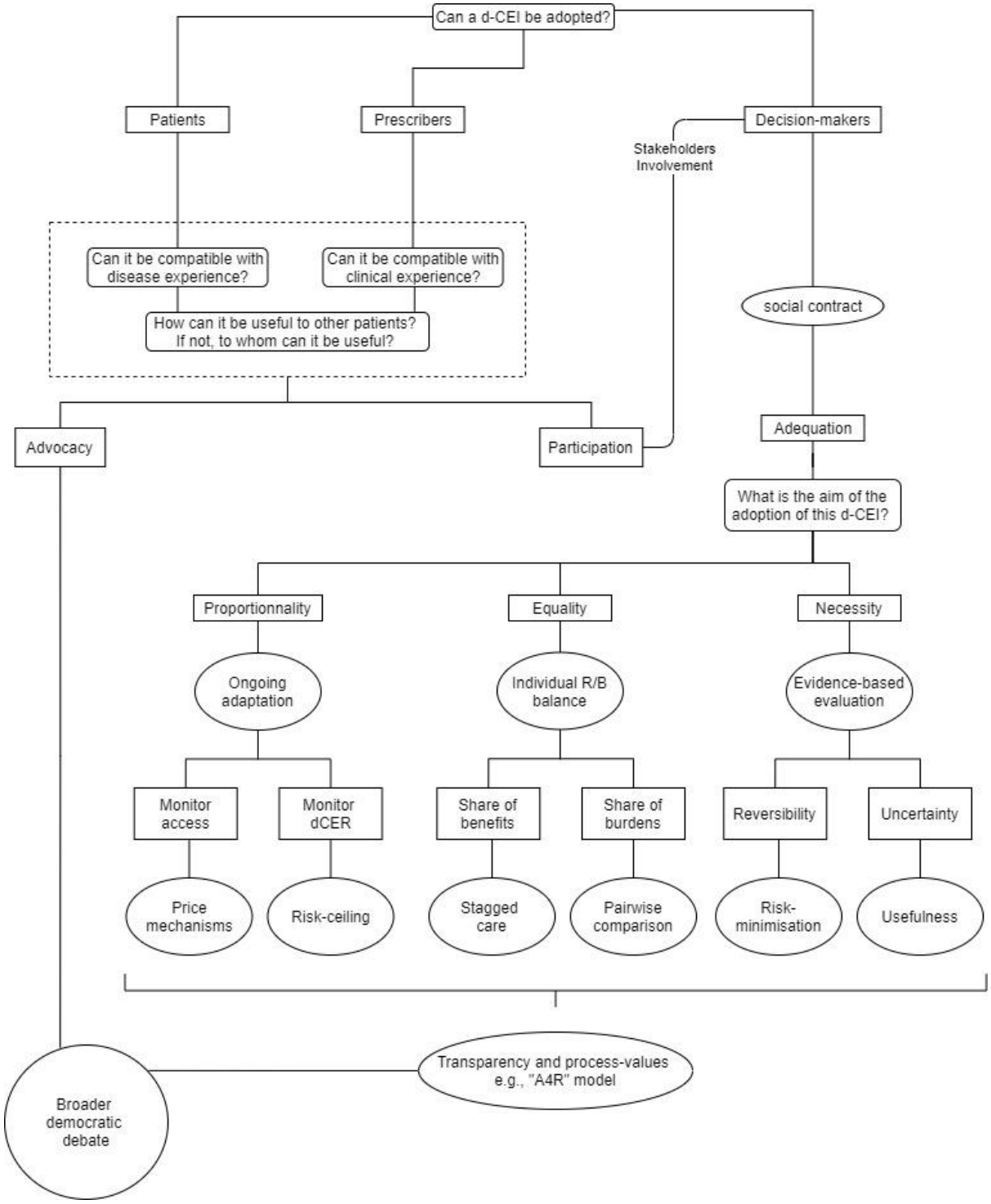


Figure 2.1: An ethical inquiry into d-CEIs adoption conditions

3- A political economy inquiry

Research by P. Smith and S. Hawk on the 'political economy' of healthcare systems, which analyses the interplay between experts and decision-makers, has been very influential and constitutes a major source of inspiration for this third inquiry into d-CEIs adoption. The first section illustrates how different types of healthcare systems may facilitate or hinder d-CEIs' adoption. It also identifies the different stakeholders' perspectives that decision-makers face, in order to identify those who could either support d-CEIs' adoption or object to it. Section 3.2 surveys current HTA agencies processes and their (or lack of) recommendations regarding d-CEIs. Section 3.3 turns to specific d-CEIs which illustrate the difficulty in precisely defining their perimeter. Section 3.4 reviews the different methods used to analyse decision-makers perspectives and the findings drawn from other fields of application or other related topics, in the absence of direct evidence on d-CEIs.

3.1 – System characteristics and stakeholders' perspectives on d-CEIs

3.1.1 - System characteristics

How would healthcare systems' characteristics influence the probability of adoption of d-CEIs? In the absence of literature to address this question, we concentrate on three main system characteristics (the type of financing, the type of regulation, and the structure of healthcare expenditure) to identify a number of hypotheses as to how these characteristics might influence the adoption probability.

Health care services can be financed by individuals themselves and/or by third party payers which can be public (government) or private (insurers, employers, charities)[25]. For example, out-of-pocket payments, which are defined by the World Health Organisation as "direct payments made by individuals to health care providers at the time-of-service use", vary between countries. It is reasonable to assume that the way a country's health system is financed is likely to influence the probability of d-CEI adoption. The direction of this influence remains uncertain and should be tested. While it is likely that countries with high out-of-pocket payments, such as Greece or Bulgaria for example, may be more willing to adopt d-CEIs because the cost reduction will mostly accrue to

[25] Deber, R., Hollander, M. J., & Jacobs, P. (2008). Models of funding and reimbursement in health care: a conceptual framework. *Canadian Public Administration*, *51*(3), 381-405.

patients, it is unsure whether countries with lower out-of-pocket payments will show a lesser willingness to adopt d-CEIs; and both hypotheses should be tested.

The second characteristic identified is the type of health system regulation or governance. WHO defines the regulation as "a key means by which a government gives effect to its policy preferences, especially through the exercise of a government's law-making power"[26]. In a health system, the relationship between beneficiaries, funding bodies, and service providers must be regulated[27]. It is reasonable to assume that the way a country's health system is regulated is likely to influence d-CEIs' adoption. Indeed, the more State regulated the healthcare system, the easier it might be to adopt d-CEIs.

The third characteristic that may influence the probability of d-CEI adoption is the structure of health expenditure. Wendt and al. (2009)[28] distinguish three types of healthcare expenditure: inpatient, outpatient and preventive expenditures. It is possible that countries that spend more on prevention, such as Italy, will more readily adopt d-CEIs (such as non-pharmaceutical interventions). They are more accustomed to considering the long-term opportunity cost than countries that focus on providing the latest technology in health care.

This analysis of system characteristics is by no way exhaustive but indicates how hypotheses could be defined in respect to d-CEIs' adoption and possibly tested in future research.

3.1.2 - Stakeholders' perspectives on d-CEIs

Priority setting[29] is "the process of making decisions about how best to allocate limited resources to improve population health"[30]. It takes place in a highly political context, in which many different

[26] Clarke, D. (2016). Law, regulation and strategizing for health. *Strategizing national health in the 21st century: a handbook. Geneva: World Health Organization*.

[27] Böhm, K., Schmid, A., Götze, R., Landwehr, C., & Rothgang, H. (2013). Five types of OECD healthcare systems: empirical results of a deductive classification. Health Policy, 113(3), 258-269.

[28] Wendt, C., Frisina, L., & Rothgang, H. (2009). Healthcare system types: a conceptual framework for comparison. *Social Policy & Administration*, *43*(1), 70-90.

[29] " Hauck, K., & Smith, P. C. (2015). The politics of priority setting in health: a political economy perspective. *Center for Global Development Working Paper*, (414)."

[30] Terwindt F. Priority-setting for national health policies, strategies and plans. Soucat A, editor. World Health Organization; 2016.

political interest groups seek to take part[31]. Stakeholders or interest groups can be defined as "any institutionalized organization that engages in political activity relative to the process of making or influencing policy without explicitly trying to obtain or exercise the responsibility of government"[32]. Thus, the implementation of d-CEIs is further complicated by the fact that many actors are involved in setting health system priorities. Stakeholders may pursue various objectives that may evolve over time. They may support or oppose the implementation of d-CEIs at different times. The misalignment of their fluctuating interests and the conflict of individual and collective perspectives lay at the root of the lack of implementation of d-CEIs by decision-makers.

One challenging characteristic of d-CEIs is that there is no specific interest group to support this type of intervention. The theory of organized / disorganized interest groups has been used to explain underinvestment in public health policies and it carries over to d-CEIs. According to Olsen (1997), "Because the potential beneficiaries of public health actions are unknown and may not even yet be born, public health policies, by design, have no clear apparent constituency to support it"[33]. Preventive public health interventions are a good example: the beneficiaries are at a disadvantage because there is no clearly defined patient group lobbying in their favour, and they have to rely on individuals or groups with altruistic motivation for support. Further evidence of the importance of support groups is given by the fact that FDA drug approval times are shorter for drugs with more active and wealthier disease-interest groups[34] and that have media-friendly interest when compared with interventions aimed at the whole population, or at large and difficult to delineate subgroups of individuals at risk, such as preventive screening or healthy lifestyle campaigns. This view can be fruitfully applied to understand d-CEIs' lack of adoption, although they present one additional challenge: the fact that the improvement for the whole population will necessarily imply a loss of clinical benefits for some.

[31] Hauck, K., Thomas, R., & Smith, P. C. (2016). Departures from cost-effectiveness recommendations: the impact of health system constraints on priority setting. *Health Systems & Reform*, *2*(1), 61-70.

[32] Contandriopoulos, D. (2011). On the nature and strategies of organized interests in health care policy making. *Administration & society*, *43*(1), 45-65.

[33] Glied, S. (2008). Public Health and Economics: Externalities, Rivalries, Excludability, and Politics. The Contested Boundaries of American Public Health. J. Colgrove, G.

[34] Carpenter, M. A. (2002). The implications of strategy and social context for the relationship between top management team heterogeneity and firm performance. *Strategic Management Journal*, *23*(3), 275-284.

1 - Patients and their representatives

Patients are the first to be affected by the adoption of d-CEIs. As a result, measuring the health loss as perceived by the patient population, rather than by health care professionals, is essential, as illustrated in the case study outlined below (section 3.4.6) that underlines the importance of considering patients' preferences, as systematic decision-making simply based on relative costs and the point of view of the insurer could lead to an inefficient use of public funds. This example shows the need to fully document all possible dimensions and perspectives when considering to adopt d-CEIs. On the other hand, it also shows that if the health loss assessment is carried out from the perspective of the patient, there is a risk that the d-CEI will not be adopted. If patients have to make their own choice, it is likely that they will systematically choose the most expensive option, all the more if they have a generous cover. The level of out-of-pocket payment (OOP)[35] varies across countries and will have an impact on patients' willingness to accept a d-CEI.

Patient organisations play an important role in the adoption (or non-adoption) of certain interventions, sometimes even when there are doubts about their cost-effectiveness or even their clinical effectiveness and safety. Berg (2006)[36] illustrates this with the example of the breast cancer drug Herceptin in the English National Health Survey (NHS).

2 - Healthcare professionals

Healthcare professionals are other key stakeholders[37] who may oppose the implementation of d-CEIs. Indeed, healthcare professionals have an obligation of means and therefore focus on the individual well-being and they are reluctant to consider the collective perspective in their decisions[38].

[35] Hassenteufel, P., Benamouzig, D., Minonzio, J., & Robelet, M. (2017). Policy diffusion and translation: the case of evidence-based health agencies in Europe. *Novos estudos CEBRAP*, *36*(1), 77-96.

[36] Berg, S. (2006). Herceptin: Was patient power key? *BBC News*, *9*.

[37] Hauck, K., Smith, P. C., & Goddard, M. (2004). The economics of priority setting for health care: a literature review.

[38] Polisena, J., Clifford, T., Elshaug, A. G., Mitton, C., Russell, E., & Skidmore, B. (2013). Case studies that illustrate disinvestment and resource allocation decision-making processes in health care: a systematic review. *International journal of technology assessment in health care*, *29*(2), 174.

Some researchers, as Harris et al (2017)[39] argue that there is a lack of common understanding of terminology and concepts in policymaking and that this creates problems for successful decision-making, and adaptation of policy change. d-CEIs are often wrongly associated with rationing and can be perceived by health professionals as an attack on their profession's freedom to choose an adequate treatment[40]. When conflated with rationing, d-CEIS can then be Xviewed as reducing patient choice instead of widening the range of treatment options.

3 - Pharma/device companies

The pharmaceutical industry is another powerful stakeholder that may favour certain health interventions and drug treatments over others. The acceptance of d-CEIs by policy makers is not in the interest of this industry since d-CEIs are often cheaper. As in other fields, such as the food industry, powerful interest groups are present and may influence the decision to adopt D-CEIs.

4 - Media

As shown during the Covid-19 crisis and the case of the Astra Zeneca vaccine (see section 3.4 below), the media play an important role in debates on setting health system priorities. Indeed, European countries "*face difficulties in putting these debates on a rational basis and limiting media and lobby power, with implications for the values that underpin decisions*" (Teutsch and al., 2012)[41].

5 – Decision-makers

In the priority-setting process, policymakers have to align the preferences and interests of all stakeholders and accommodate diverse constraints in their decisions, even if it implies departing from welfare maximizing solutions (Hauck and Smith, 2015; Goddard et al., 2006: 81, Hauck et al., 2016). It is often the reality of the political decision-making process that mitigates backing for appropriate health investments, rather than the methodological shortcomings of CEA**.** Indeed, even

[39] Harris, C., Green, S., Ramsey, W., Allen, K., & King, R. (2017). Sustainability in Health care by Allocating Resources Effectively (SHARE) 1: Introducing a series of papers reporting an investigation of disinvestment in a local healthcare setting.

[40] Mitchell, D., Bowles, K. A., O'Brien, L., Bardoel, A., & Haines, T. (2021). Health care staff responses to disinvestment—A systematic search and qualitative thematic synthesis. *Health care management review*, *46*(1), 44-54.

[41] Teutsch, S., & Rechel, B. (2012). Ethics of resource allocation and rationing medical care in a time of fiscal restraint-US and Europe. *Public Health Reviews*, *34*(1), 15.

though economic evaluation offers a powerful approach to setting priorities, there may be alternative perspectives from which it is rational for decision-makers to disregard CEA recommendations. Various models, such as voting models or bureaucratic decision-making, seek to explain why political decision-making process fails to generate seemingly welfare-improving policy-changes based on (Hauck and Smith, 2015; Hauck et al., 2016).

In the healthcare system, the main responsibilities to make priorities and allocate resources are placed on meso-level budget-holders (Smith, 2014). It is at this meso-level that local priority setters are responsible for resource allocation and decision-making. These decision-makers are accountable for the local population and have to show coherence with the higher macro-political expectations and frameworks. It is also at the local level, that "disinvestment initiatives" (Harris et al. 2017), including the implementation of d-CE interventions, may be more difficult to take. Unlike health professionals, national or regional health authorities do not have the legitimacy to make direct treatment choices for patients. It could therefore be argued that it is easier for regulators to recommend the adoption of d-CEIs. However, on the one hand, they need to have the support of health professionals if their recommendations and guidelines are to be effective. On the other hand, they also have to ensure the financial sustainability of health care systems. They must meet the expectations of different and sometimes conflicting stakeholders.

3.2 –HTA agencies and d-CEIs

While the overall assessment related to the clinical effectiveness of a new intervention is coordinated at EU level, the economic assessment and evaluation (including cost-effectiveness) is determined by each Member State, with considerable variations in processes and social values. Beletsi (2018) indicates that in some countries, the HTA process is characterised by a high level of maturity, while in others it is still evolving[42]. In England, for example, the National Institute for Health and Care Excellence (NICE) was established as early as 1999. In Italy, the National Agency for Regional Health Services (AGENAS) only dates back to 2006. Finally, in some countries, such as Estonia, there is no agency dedicated to the HTA process. Thus, based on a review of HTA agencies in

[42] Beletsi, A., Koutrafouri, V., Karampli, E., & Pavi, E. (2018). Comparing use of health technology assessment in pharmaceutical policy among earlier and more recent Adopters in the European Union. *Value in health regional issues*, *16*, 81-91.

Europe, Löblová (2016)[43] proposes a chronological taxonomy of these agencies. The forerunner countries are those that have traditionally set the trends in health policy. In these countries, HTA agencies have evolved over time and they have experimented with different jurisdictions and designs of HTA agencies. The mainstreamers are those countries that have established their HTA bodies based on what was being done in forerunner countries. In most of these countries, HTA bodies are independent with an advisory role only. Finally, the non-adopters are those countries that have not established HTA agencies, although there are ongoing discussions of their potential value in several of these countries.

Table 3.1: Chronological taxonomy of HTA agencies by Löblová

Forerunners: the UK (NICE 1999, SMC, 2002), Sweden (SBU, 1987), Finland (FinOHTA, 1995), Denmark (DACEHTA, 1997), Spain (COHTA – Catalonia, 1991, Osteba -Basque, 1992, AEFS – central, 1993 AETSA – Andalusia, 1996).
Mainstreamers: France (HAS 2004), Belgium (KCE, 2004), Croatia (AAZ, 2009), Germany (IQWiG, 2004), Hungary (GYEMSZI, 2004), Poland (AHTAPol, 2005), Austria (LBI, 2006), The Netherlands (CVZ, 2006), Ireland (HIQA, 2007), Italy (AGENAS, 2006), Latvia (VEC, 2009-20011)
Non-adopters: Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Lithuania, Luxembourg, Malta, Portugal, Romania, Slovakia, Slovenia.

Source: Löblová (2016)44

While d-CEIs should not be simply assimilated to rationing, as shown in section 1 of this report, they constitute a powerful lever for disinvestment, defined as "*withdrawing health resources from any existing health care practices, procedures, technologies or pharmaceuticals that are deemed to deliver little or no health gain for their cost, and thus do not represent efficient health resource allocation*"[45]. Indeed, the implementation of a d-CEI can provide health benefits at the collective level by freeing up resources that can be re-invested elsewhere. The potential of d-CEIs remains undervalued and they have received much less attention from HTA bodies than their counterparts

[43] Löblová, O. (2016). Three worlds of health technology assessment: Explaining patterns of diffusion of HTA agencies in Europe. Health Economics, Policy and Law, 11(3), 253-273. doi:10.1017/S1744133115000444

[44] Löblová, O. (2016). Three worlds of health technology assessment: Explaining patterns of diffusion of HTA agencies in Europe. Health Economics, Policy and Law, 11(3), 253-273. doi:10.1017/S1744133115000444

[45] Elshaug, A.G., Moss, J.R., Tunis, S.R. and Hiller, J.E., 2007. Challenges in Australian policy processes for disinvestment from existing, ineffective health care practices. Australia and New Zealand health policy, 4(1).

(incrementally cost-effective interventions, hereafter i-DCIs) even in forerunners. For instance, d-CEIs are not explicitly mentioned as such in the EUnetHTA *core model for screening technologies*, established and funded by the EU, in order to contribute towards a more homogenous presentation of productions by MS HTA bodies. In cases of both lower costs and lower clinical effectiveness, the EUnetHTA core model suggests that further analysis is necessary before deciding on adoption. In fact, based on its incremental cost-effectiveness ratio (ICER), a d-CEI should be considered cost-effective if the society considers that the cost savings compensate for the lower effectiveness (EUnetHTA, 2011). How society may consider that the cost savings indeed compensate for the lower effectiveness is, however, not addressed in the core model. Neither is it precisely defined in NICE[46] guidelines. A very recent review on CHTE methods[47] does indicate the need for further guidance on this specific point, but this has not yet been produced.

A long-standing methodological debate addressed in the CHTE methods review relates to the slope of the threshold to adopt in the S-W quadrant, known after Jack Dowie's 2015 paper as the 'kinked' threshold debate (see section 1 of this report). The conclusion of the CHTE methods review is that "*There was consensus around using a single threshold because it has methodological advantages, and is in agreement with NICE principles and with the ethical principle of justice. Although there is some research in support of the 'kinked' threshold, the task and finish group noted this does not apply in a context of decision making on behalf of others, such as decision making by the NICE appraisal committees.*"

Institutional differences condition networked governance (Martinsen 2020). Five clusters can be identified depending on the type of healthcare system and they are useful in predicting healthcare cooperation across the EU. Since national institutions condition who interacts with whom and who might learn from whom, we expect that d-CEIs will be more or less accepted/spread in certain healthcare clusters than others.

[46] NICE's guidelines manual states that such interventions should be recommended if they free up sufficient resources that can be re-invested in public sector care or services to increase the welfare of the population receiving care.

[47] CHTE methods review, Decision making, Task and finish group report, September 2020, item 1.4.

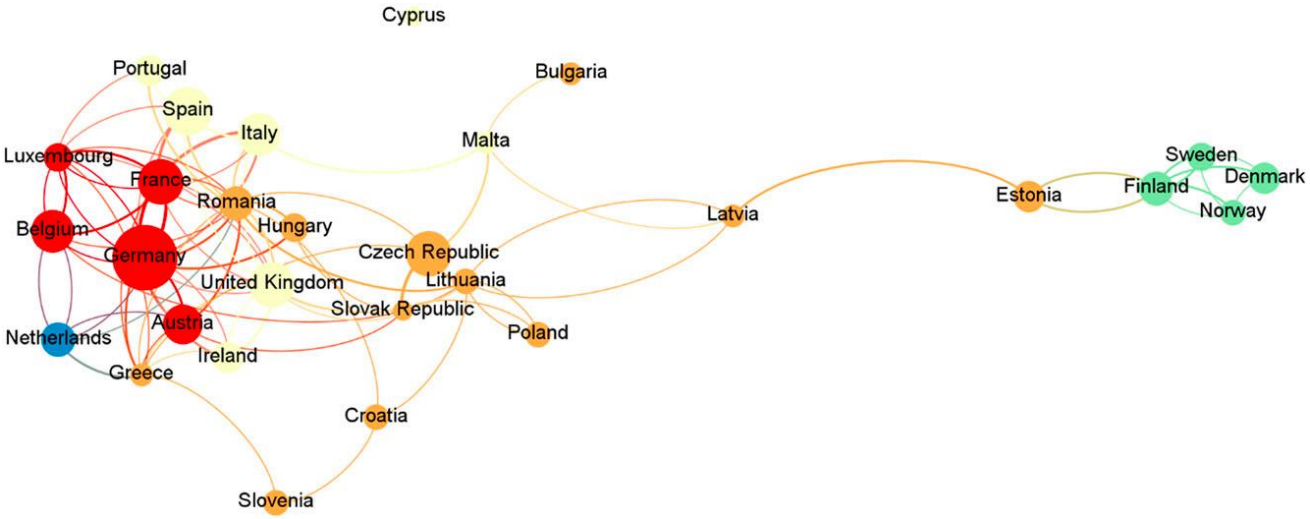


Figure 3.1: Network effect in Europe

Source: Martinsen 2020

Martinsen 2020[48] shows that there is a reinforcing tendency within clusters of countries, with some clusters of countries influencing each other more than others. If forerunner countries start implementing d-CEIs, it will increase the probability that mainstreamers (and even possibly non-adopters) will follow.

3.3 – d-CEIs case studies

Task 1 of WP11 entailed a systematic review of health economic evaluations of d-CEIs (see appendix A), which helped identify a wide selection of d-CEIs[49]. Beyond this objective of identifying main types of d-CEIs, the main results of this review show that there is an increasingly rich evidence on such interventions. The review compared the available evidence with the status of the identified d-CEIs,

[48] Martinsen, D.S., Schrama, R. and Mastenbroek, E., 2020. Experimenting European healthcare forward. Do institutional differences condition networked governance? *Journal of European Public Policy*, pp.1-22.

[49] R Scarica, X Chavez Pacheco, JCK Dupont, L Rochaix, I Durand Zaleski, M Darlington, A systematic review of decrementally cost-effective health technologies and case studies

with respect to insurance coverage or the existence of explicit guidance suggesting their use as first-line treatment recommendation. The results show a discrepancy between the availability of evidence and the adoption of d-CEIs by decision-makers in most countries. In order to illustrate this discrepancy, 6 different d-CEIs have been chosen for a more detailed presentation below. The first case study is that of ACE inhibitors versus ARBs, which illustrates how guidance has been given in some countries to follow a stepped care approach, with ACE inhibitors qualifying as d-CEIs and ARBs only offered as a second line of treatment. The next two case studies (triple therapy for rheumatoid arthritis and the rationing of access to total knee arthroplasty) directly originate from the systematic literature review and illustrate the lack of adoption, despite evidence. Physical activity is the fourth case study, selected as an illustration of a non-pharmaceutical intervention (NPI) among d-CEIs and which is increasingly adopted. The case of the Astra Zeneca vaccine is then discussed to illustrate the fluctuating nature of a d-CEI qualification. Finally, the relative value of DOXY versus ATVP is discussed in the case of malaria treatment.

1 - ACE inhibitors versus ARBs:

Converting enzyme inhibitors (ACE inhibitors) and Angiotensin receptor blockers (ARB) are two drugs that have been shown to have similar effectiveness in the treatment of high blood pressure. A systematic review of the literature on clinical studies[50] randomly comparing ACE inhibitors and ARB in hypertension prevention concluded that the clinical data does not make it possible to differentiate between ACE inhibitors and ARB in terms of antihypertensive efficacy and impact on morbidity and mortality. According to clinical data, the tolerance of ACE inhibitors and ARB is similar. A meta-analysis[51] confirms the absence of significant differences between ACE inhibitors and ARB for the severe adverse events observed. However, a dry cough that disappears after the treatment is stopped, was more frequently observed in patients taking ACE inhibitors. This side-effect is reversible and affects only a small part of the population. Apart from this difference in side effect (few patients experiencing a dry cough), the two drugs differ in their costs, as some ACE inhibitor generics are nearly half the cost than ARBs. Thus, ACE inhibitors can be considered as a

[50] Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med. 2008;148(1):16-29

[51] Reboldi G, Angeli F, Cavallini C, Gentile G, Mancia G, Verdecchia P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. J Hypertens 2008, 26:1282-9.

decrementally cost-effective intervention because they are cheaper than ARBs for very little loss of patient utility.

Instead of systematically prescribing ARB for the treatment of hypertension, the French, British and Swedish HTA bodies recommend that ACE inhibitors should be preferred as a first-line treatment for hypertension and that ARB should be reserved for patients who suffer from the side-effect[52,53,54]. These recommendations are akin to stepped care and are based on economic considerations. The Swedish HTA body indicates in its guideline that "Further reducing the blood pressure of people with moderate to high risk is more cost-effective than lowering the treatment threshold and thereby caring for more low-risk patients." In contrast, the German HTA body bases its recommendations on drug efficacy[55] and no economic considerations are made in their guidance. For example, after comparing different antihypertensive drugs, including ACE inhibitors and ARB, it recommends diuretics as a first-line treatment. In some countries, like Belgium for example, no recommendations are made by HTA bodies on the choice of ACE inhibitors as a first line of treatment.

2 - Triple Therapy versus biosimilars (bDMARDs)

After the failure of monotherapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in the treatment of rheumatoid arthritis, a chronic inflammatory disease, there are two possible treatments: triple therapy (TT), a therapy combining three conventional synthetic antirheumatic drugs (methotrexate, sulfasalazine, and hydroxychloroquine), or biosimilars (biological disease-modifying antirheumatic drugs - bDMARDs). An American multicenter and double-blind RCT[56] has shown that TT is non-inferior to Etanercept–Methotrexate therapy for patients with active rheumatoid arthritis who have failed csDMARD monotherapy. However, problems related to tolerance and non-adherence to treatment are observed with TT. Indeed, TT is associated with a higher number of gastrointestinal adverse events that resolve on

[52] Haute Autorité de Santé, Fiche « Bon usage des médicaments », Traiter l'hypertension artérielle essentielle non compliquée - Comment choisir entre IEC et sartans ? 2008

[53] NICE guideline, Renin-angiotensin system drugs: dual therapy, 2015

[54] Moderately elevated blood pressure. A report from SBU, The Swedish Council on Technology Assessment in Health Care. J Intern Med. 1995;238 Suppl 737:1-225. PMID: 9422043.

[55] Institute for Quality and Efficiency in Health Care (IQWiG), Different antihypertensive drugs as first line therapy in patients with essential hypertension, 2009 https://www.ncbi.nlm.nih.gov/books/NBK84150/

[56] O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. New England Journal of Medicine. 2013 Jul 25;369(4):307–18.

discontinuation[57,58], and its lower efficacy is likely to increase long-term costs (increased hospitalizations and joint surgeries) and indirect costs (work absenteeism)[59]. The two treatments differ in cost. While bDMARDs have been among the top 10 best-selling drugs over the past decade, TT remains significantly less expensive for those who fail csDMARD monotherapy. Taking all these elements into account, TT can be considered a decrementally cost-effective intervention[60].

Despite international recommendations encouraging consideration of TT in the event of failure of csDMARD monotherapy for the treatment of rheumatoid arthritis[61,62], there are differences in the adoption of TT across countries. According to data from the Caisse Nationale de l'Assurance Maladie (Cnam), the use of triple therapy in France is less than 1% of the 223,000 patients on long-term care (ALD) for rheumatoid arthritis. While in the UK, a national clinical audit in 2016 reported that in a sample of 2,936 patients diagnosed with rheumatoid arthritis, at least 46% of patients received a combination of csDMARDs during the first three months[63].

[57] Kaló Z, Vokó Z, Östör A, Clifton-Brown E, Vasilescu R, Battersby A, et al. Patient access to reimbursed biological disease-modifying antirheumatic drugs in the European region. Journal of Market Access & Health Policy. 2017 Jan 1;5(1):1345580.

[58] Quach LT, Chang B-H, Brophy MT, Soe Thwin S, Hannagan K, O'Dell JR. Rheumatoid arthritis triple therapy compared with etanercept: difference in infectious and gastrointestinal adverse events. Rheumatology (Oxford). 2017 Mar 1;56(3):378–83.

[59] Mary J, Bandt MD, Lukas C, Morel J, Combe B. Triple Oral Therapy Versus Antitumor Necrosis Factor Plus Methotrexate (MTX) in Patients with Rheumatoid Arthritis and Inadequate Response to MTX: A Systematic Literature Review. The Journal of Rheumatology. 2017 Apr 15;jrheum.160643.

[60] Bansback N, Phibbs CS, Sun H, O'Dell JR, Brophy M, Keystone EC, et al. Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. Annals of Internal Medicine. 2017 Jul 4;167(1):8.

[61] 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis - Singh - 2016 - Arthritis & Rheumatology - Wiley Online Library [Internet]. [cited 2019 Apr 23]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/art.39480

[62] EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. - PubMed - NCBI [Internet]. [cited 2019 Apr 23]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28264816

[63] *Firth J, Snowden N, Ledingham J, Rivett A, Galloway J, Dennison EM, et al. The first national clinical audit for rheumatoid arthritis. Br J Nurs. 2016 Jun 9;25(11):613–7.*

These disparities within European countries can, firstly, be explained by differences in the eligibility criteria for reimbursement of bDMARDs. In France, the eligibility criteria that patients must meet for claiming reimbursement of bDMARDs do not entail a minimum duration of disease or failure of a certain number of front-line csDMARDs treatments. Similarly, in Germany, biosimilars are fully reimbursed. In other European countries such as the United Kingdom, reimbursement requires a minimum DAS28 score >3.2, disease duration of more than 6 months, and failure of at least one or more csDMARDs[64].

These disparities in the implementation of TT, within European countries, can also be explained by differences in the recommendations of the HTA bodies. NICE, the UK's health technology assessment body, recommends TT when the therapeutic goal of csDMARD monotherapy has failed in the treatment of rheumatoid arthritis[65]. bDMARDs are only recommended if csDMARD monotherapy and TT have failed. In constrast, the German HTA authority encourages the use of biosimilars. While the various assessments of the German HTA authority identify recommendations for the treatment of rheumatoid arthritis[66,67] with drugs and take efficacy into account in their studies, the question of their cost is never asked. In France, TT is not a standard treatment for rheumatoid arthritis and although an economic evaluation[68], conducted by the Haute Autorité de Santé, shows that TT is the least expensive second-line treatment, no recommendation is made on its use and the report calls for further studies on patient compliance with TT. Similarly, in Belgium and Sweden, no recommendations are made by the respective HTA body on the use of TT or biosimilars in second-

[64] Kaló Z, Vokó Z, Östör A, Clifton-Brown E, Vasilescu R, Battersby A, et al. Patient access to reimbursed biological disease-modifying antirheumatic drugs in the European region. Journal of Market Access & Health Policy. 2017 Jan 1;5(1):1345580.

[65] NICE guidelines, Rheumatoid Arthritis in Adults: Diagnosis and Management, 2018.

[66] Institute for Quality and Efficiency in Health Care (IQWiG), Biotechnologically produced drugs as second-line therapy for rheumatoid arthritis: Executive summary of final report A10-01, Version 1.0. 2013 Jun 28. PMID: 24783297. https://pubmed.ncbi.nlm.nih.gov/24783297/

[67] Institute for Quality and Efficiency in Health Care (IQWiG), Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Rheumatoide Arthritis, 2016, https://www.iqwig.de/en/projects/v14-02.html

[68] Haute Autorité de Santé, Évaluation médico-économique des traitements de fond biologiques dans la prise en charge de la polyarthrite rhumatoïde, 2019

line treatment of rheumatoid arthritis. In Sweden, recommendations have been made by the Sweden National Board of Health and Welfare[69].

3 - Rationing access to Total Knee Replacement (TKR)

Total knee replacement (TKR) is a surgical procedure to replace a diseased knee with an artificial prosthesis. Rationing access to TKR aims to avoid surgery for patients who would obtain little or no benefit from surgery, and is implemented by narrowing the eligibility criteria according to a functional scale. Even if rationing of access to TKR interventions can be cost saving[70], alternative non-pharmacological and pharmacological treatments could be less effective than surgery. Given these findings, rationing access to TKR can be considered as decrementally cost-effective interventions.

Very few clinical guidelines of HTA agencies in Europe have identified indication criteria for surgery using threshold values. In countries with universal healthcare systems such as the UK and Finland, the demand for joint replacement is managed by waiting lists[71]. In the UK, access to TKR is often rationed based on patient characteristics, such as age and functional assessments. The Oxford Knee Score (OKS) is used in some British regions to define threshold values above which patients are not eligible for surgery[72]. In many practices in the UK, TKR is commissioned when OKS is ≤23 (0 to 48 scoring system), the patient is fit for surgery with a BMI ≤35, and a non-smoker[73]. Although the HAS

[69] Socialstyrelsen. (2012). Nationella riktlinjer för rörelseorganens sjukdomar 2012, https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2012-5-1.pdf

[70] Impact of total knee replacement practice: cost effectiveness analysis of data from the Osteoarthritis Initiative | The BMJ [Internet]. [cited 2019 Apr 23]. Available from: https://www.bmj.com/content/356/bmj.j1131

[71] Explaining Waiting Times Variations for Elective Surgery Across OECD Countries [Internet]. 2003 Oct [cited 2019 Apr 23]. Report No.: 7. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/explaining-waiting-times-variations-for-elective-surgery-across-oecd-countries_406746186162

[72] Eibich P, Dakin HA, Price AJ, Beard D, Arden NK, Gray AM. Associations between preoperative Oxford hip and knee scores and costs and quality of life of patients undergoing primary total joint replacement in the NHS England: an observational study. BMJ Open. 2018 Apr 1;8(4):e019477.

[73] hip-and-knee-arthroplasty.pdf [Internet]. [cited 2019 May 16]. Available from: https://www.harrogateandruraldistrictccg.nhs.uk/data/uploads/rss2/hip-and-knee-arthroplasty.pdf

identifies certain factors, such as a high body mass index, as likely to limit the survival of the implant, no threshold is retained in France.

4 - Physical activity

Despite the growing interest in Non-Pharmacological Interventions (NPIs)[74], their scope and definition may appear somewhat nebulous. Indeed, there is not a consensus today about the scope, limitations, registry, and precise definition. The World Health Organization (WHO), in its *Traditional Medicine Strategy for 2014-2023*, introduces a difference between traditional and complementary medicine. The complementary or alternative medicine (which includes NPIs) *"refers to a broad set of health care practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant health-care system"*. Under this definition, a given practice can be considered as a traditional medicine in a country while it would be complementary in another. The CEPS Plateform in France[75] proposes to define NPIs as "*science-based and non-invasive interventions on human health. They aim to prevent, care, or cure health problems. They may consist of products, methods, programs, or services whose contents are known by users. They are linked to biological and/or psychological processes identified in clinical studies. They have a measurable impact on health, quality of life, behavioral and socioeconomic markers. Their implementation requires relational, communicational and ethical skills*"[76]. In this definition, NPIs are notably no longer considered in opposition to dominant biomedical practices but defined as interventions whose main characteristic is simply being outside the scope of conventional and reimbursed health interventions.

While they have been considered for a long time as intrinsically complementary, with a prescription made jointly with or after the initiation of a pharmacological, surgical or radiation treatment, there

[74] Reiter, B., Baumhofener, F., Dlaboha, M., Madsen, J., Regenfelder, S., Weidenhammer, W. (2012). CAMbrella strategy for dissemination of project findings and future networking. Vienna: Viennese Academy for Integrative Medicine.

[75] The collaborative University Platform dedicated to the evaluation of Health Prevention Programs and Supportive Care (Plateforme CEPS) of the universities of Montpellier.

[76] Ninot, G., Boulze-Launay, I., Bourrel, G., Gérazime, A., Guerdoux-Ninot, E., Lognos, B., Libourel, T., Mercier, G., Oude, A., Rapior,S., Senesse, P., Trouillet, R., Carbonnel, F. (2018). De la définition des interventions non médicamenteuses à leur ontologie. *HEGEL [ISSN 2269-0530], 2018, 01*.

are situations in which NPIs can be prescribed as a substitute[77]. In fact, when vaccines or drugs are scarce or even unavailable, NPIs – in the form of preventative attitudes such as avoiding close contacts – can be the only way to fight against influenza by delaying the epidemic[78]. For that matter, the term "non-pharmacological interventions" should be preferred over other denominations as they can either be a treatment *per se* or a complement to prevent, care or cure a health problem. Thus, NPIs can be part of a stepped care approach. Donovan and Marlatt (1993)[79] indicate that adopting a stepped care approach implies that "*the least costly, least intensive, and least restrictive treatment judged sufficient to meet the person's needs and goals should be attempted initially before more costly and restrictive treatments are attempted*"[80]. In this approach, treatment is tailored to individual in order to provide the appropriate level of care[81]. Firstly, a low-intensity intervention is given to all patients. Patients who do not respond to this intervention will receive more intensive treatment. In a resource-constrained context, the stepped care approach takes advantage of the fact that different patients require different levels of care. Conversely, at higher levels of treatment, patients who are progressing well through the disease can step down to a lower level of care. Thus, stepped care has been advocated for managing various chronic diseases[82].

While not all NPIs are d-CEIs, as some interventions can sometimes be more expensive than conventional care, others, like physical activity, are d-CEis. Physical activity is an NPI defined by WHO as "*any bodily movement produced by skeletal muscles that require energy expenditure*". The scientific literature on the benefits of physical activity on health (mental and physical) is robust and covers several indicators (life expectancy, morbidity, quality of life), with an extensive coverage of

[77] HAS. (2011). Développement de la prescription de thérapeutiques non médicamenteuses validées. *Paris: HAS Edition*.

[78] World Health Organization. (2019). *Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza: annex: report of systematic literature reviews* (No. WHO/WHE/IHM/GIP/2019.1). World Health Organization.

[79] Donovan DM, Marlatt GA. Recent developments in alcoholism behavioral treatment. Recent Dev Alcoholism 1993;11:397-411.

[80] Donovan, D. M., & Marlatt, G. A. (1993). *Behavioral Treatment* (pp. 397–411). Springer, Boston, MA. https://doi.org/10.1007/978-1-4899-1742-3_21

[81] Bower, P., & Gilbody, S. (2005). Stepped care in psychological therapies: access, effectiveness and efficiency: narrative literature review. *The British Journal of Psychiatry*, *186*(1), 11-17.

[82] Von Korff, M., & Tiemens, B. (2000). Individualized stepped care of chronic illness. *Western Journal of Medicine*, *172*(2), 133.

diseases[83]. It improves life expectancy, reduces premature mortality and the risk for many diseases (cancer, diabetes, obesity, depression, anxiety). According to the WHO, lack of physical activity is the fourth leading cause of death in the world. A literature review was conducted on the cost-effectiveness of physical activity in the health treatment of chronic diseases[84]. In some cases, physical activity interventions are dominant (cheaper and more effective than the comparator)[85,86] but can sometimes be considered as decrementally cost-effective interventions[87].

Physical activity can be prescribed as a complementary or even primary treatment for certain chronic diseases (type 2 diabetes, hypertension, overweight, etc.). Thus, in several countries such as Sweden or the United Kingdom, physical activity can be prescribed for at-risk and chronically ill patients. In France, the French National Authority for Health recommended in 2011 the prescription of non-medicinal therapies, including physical activity, as a complementary or alternative strategy to a drug prescription[88]. However, it was not until the Health Law of January 2016 that general practitioners were able to prescribe physical activity to patients with long-term conditions[89]. The funding of the '*As du Cœur*' project as part of the recent innovative payment experiments (Article 51) in 2018 in France shows that the potential of physical activity is increasingly recognized by health

[83] Elsa Perdrix, Sport et santé : une méta-analyse, recto-verso n°1, *site Hospinnomics.*

[84] Guillon, M., Rochaix, L., & Dupont, J. C. K. (2018). Cost-effectiveness of interventions based on physical activity in the treatment of chronic conditions: a systematic literature review. *International journal of technology assessment in health care*, *34*(5), 481-497.

[85] Aboagye E, Karlsson ML, Hagberg J, Jensen I. Cost-effectiveness of early interventions for non-specific low back pain: A randomized controlled study investigating medical yoga, exercise therapy and self-care advice. J Rehabil Med. 2015;47:167-173.

[86] Mazari FAK, Khan JA, Carradice D, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. Br J Surg. 2013;100:1172-1179.

[87] Reed, S. D., Whellan, D. J., Li, Y., Friedman, J. Y., Ellis, S. J., Pina, I. L., ... & HF-ACTION Investigators. (2010). Economic evaluation of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) randomized controlled trial: an exercise training study of patients with chronic heart failure. *Circulation: Cardiovascular Quality and Outcomes*, *3*(4), 374-381.

[88] Haute Autorité de Santé (2011). Développement de la prescription de thérapeutiques non médicamenteuses validées.

[89] Haute Autorité de Santé. Prise en charge de l'hypertension artérielle de l'adulte. Saint-Denis La Plaine: HAS; 2016.

care providers, in this case for patients who have had an acute cardiac episode. Finally, physical activity can play a role in the tertiary prevention of certain diseases. For example, in the case of cancer, it helps reduce the undesirable side-effects of treatments at induction or later on[90].

5 - AstraZeneca Vaccine

On 29 January 2021, the AstraZeneca® Covid-19 Vaccine was granted conditional marketing authorization in Europe. This vaccine was the third to be authorized in Europe to prevent Covid-19 caused by SARS-CoV-2 in people aged 18 years and over. Does it qualify as a d-CEI? Qualifying an intervention as "decrementally cost-effective" is not final, as scientific knowledge about the effectiveness and adverse effects of an intervention may change over time. Thus, as illustrated by the example of the AstraZeneca vaccine, an intervention may be considered decrementally cost-effective at one point in time, but not be considered so later. When the AstraZeneca vaccine was authorized in Europe, there were only two other vaccines (Pfizer and Moderna). Existing data indicated that the AstraZeneca vaccine was less effective than the other two vaccines for certain subgroups of the population. AstraZeneca's efficacy data are from three phase II/III clinical trials involving 16,437 volunteers. They concluded an efficacy of 62% to 70% in people under 65 years of age, compared to 93.5% efficacy for the Moderna vaccine and 95% for the Pfizer vaccine[91]. However, the AstraZeneca vaccine had some advantages. Its less restrictive storage conditions compared to Moderna and Pfizer vaccines facilitated the vaccination process and increased the daily vaccination capacity. In addition, the AstraZeneca vaccine was priced much lower than the other two vaccines. The average selling price in March 2021 for two doses of vaccine, i.e., a full vaccination, was €6 for AstraZeneca, and €31 for Pfizer and Moderna. AstraZeneca could therefore be considered as a decrementally cost-effective intervention: a less expensive intervention but also slightly less effective than existing interventions. However, the Janssen vaccine was granted conditional marketing authorization in Europe on 11 March 2021, reducing the relative benefits of the AstraZeneca vaccine in terms of storage conditions. Indeed, this vaccine is packaged in ready-to-use multi-dose containers that can be stored for up to 3 months under standard refrigerated conditions

[90] Speck, R. M., Courneya, K. S., Mâsse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. Journal of Cancer Survivorship, 4(2), 87-100.

[91] Haute Autorité de Santé, 2 février 2021, AstraZeneca : la HAS recommande son utilisation chez les professionnels de santé et les personnes de 50 à 64 ans

(2-8°C). In addition, vaccinated individuals are protected 14 days after vaccination and do not need to return for a second dose.

Due to the rapid evolution of scientific knowledge about the effectiveness, adverse effects and organizational characteristics of an intervention, decisions taken by policymakers regarding a decrementally cost-effective intervention are not to be taken as final and are therefore likely to be adjusted over time. Thus, in the case of the AstraZeneca vaccine, the Haute Autorité de Santé (HAS) recommendations changed several times when new scientific knowledge was acquired about the vaccine. On February 2nd 2021, based on the scientific knowledge available at that time, HAS recognized the efficacy of AstraZeneca vaccine against symptomatic forms of Covid-19 and issued its first recommendations[92]. Due to inconclusive data on vaccine efficacy on population groups aged 65 and over, HAS recommended the AstraZeneca vaccine for those under 65. On March 1st, 2021, HAS modified its recommendations for the AstraZeneca vaccine in the light of new preliminary data on the impact of AstraZeneca vaccination on hospital admissions for the elderly in Scotland[93]. After suspending vaccination like several other European countries (Denmark, Norway, Iceland, the Netherlands, Germany, Italy, Spain, Portugal and France), in mid-March, following the occurrence of serious thromboembolic and haemorrhagic events among those vaccinated with the AstraZeneca vaccine, HAS modified again its recommendations on March 19th, 2021.[94] Based on new data provided by the European Medicines Agency (EMA)[95], HAS recommends the use of the AstraZeneca vaccine only for people aged 55 and over. The uncertainty about effectiveness and risk which always surrounds the production of recommendations, was exacerbated by the need for rapid implementation of measures to fight the epidemic.

[92] Décision n° 2021.0031/DC/SEESP du 2 février 2021 du collège de la Haute Autorité de santé portant adoption de la recommandation vaccinale intitulée « Stratégie de vaccination contre la Covid-19 - Place du Covid-19 Vaccine AstraZeneca »

[93] Avis n° 2021.0008/AC/SEESP du 1er mars 2021 du collège de la Haute Autorité de santé sur l'efficacité du vaccin AstraZeneca chez les personnes âgées au vu des données préliminaires soumises au BMJ sur l'impact de la vaccination en Ecosse sur les hospitalisations

[94] Avis n° 2021.0018/AC/SEESP du 19 mars 2021 du collège de la Haute Autorité de santé sur la place du vaccin AstraZeneca dans la stratégie vaccinale suite à l'avis de l'agence européenne des médicaments concernant des évènements indésirables survenus dans plusieurs pays européens chez des personnes vaccinées

[95] European Medicines Agency. COVID-19 vaccine AstraZeneca suspension for injection. COVID-19 vaccine (ChAdOx1-S [recombinant]). Summary of product characteristics. Amsterdam: EMA; 2021.

In the case of the AstraZeneca vaccine, the political decision is whether or not to administer a vaccine that is less expensive but also less effective against the variants[96] and with minimal risks of thrombosis. However, as the media has seized the subject and the debate fell into the public domain, everyone was able to give their opinion on a very complex subject, sometimes with limited background knowledge and without robust and well-documented arguments. In France, the debate has been cast by considering the individual benefit/risk ratio rather than adopting a population approach, which is the level at which policy-makers are expected to consider the adoption of decrementally cost-effective interventions. It is interesting to note that, although transparency on the benefits and risks of vaccines is a legal and ethical requirement in health democracies, it did not contribute to simplifying the trade-offs faced by policy-makers, in fact, quite the contrary, and many potential beneficiaries keep insisting on being given the choice of vaccine.

6 – DOXY versus ATVP in Malaria

Atovaquone-Proguanil (ATVP) and Doxycycline (DOXY) are the recommended first-line treatments in France for preventing P. falciparum malaria in travelers to endemic areas. Both requiring a daily intake during and after the travel, the two antimalarials display a high and comparable efficacy. Moreover, adverse events appear with a similar frequency in ATVP users and DOXY users. As recommended by French national guidelines, the choice among the two treatments depends on tolerance, simplicity of the administration schedule, and the financial resources of travelers. ATVP has become the reference chemoprophylaxis for travelers in areas of chloroquine-resistance since it is well tolerated and requires continuation of treatment only one week after returning, unlike DOXY, which requires one month of treatment after returning. However, the price of ATVP is the highest among all available drugs. A treatment with DOXY, while being available at a very moderate price (around 70% lower than that of ATVP), needs to be pursued thirty days after the return and, as the

[96] Haute Autorité de Santé. Stratégie vaccinale contre la Covid-19 : impact potentiel de la circulation des variants du SARS-CoV-2 sur la stratégie. Saint-Denis La Plaine: HAS; 2021

[96] Camilla Fiorina (2020), master thesis, "Evaluating the consequences of reimbursing malaria chemoprophylaxis to travelers departing from metropolitan France to highly endemic areas of sub-Saharan Africa: A cost effectiveness analysis"

half-life[97] of doxycycline is short, a strictly daily intake at the same time of the day is essential, especially after returning. Consequently, it has been estimated that only 44% of DOXY users are fully compliant with their treatment[98], with respect to 70% of ATVP users. Low adherence rates are the main obstacle to chemoprophylaxis's effectiveness, as only fully compliant users are protected from malaria.

A recent study has assessed the medico-economic consequences of reimbursing 65% of the cost of recommended chemoprophylaxis to French travelers heading to endemic areas of Sub-Saharan Africa[99]. The reimbursement has the objective of improving imported malaria prevention in France, which is the industrialized country with the highest number of annually imported malaria cases. By reducing the cost of the preventive treatment, which is currently fully paid for by travelers, a similar policy could be an important incentive for medication intake. Following the guidelines of the Haute Autorité de Santé for appraisal of public health policies, the evaluation was made from the perspective of the French National Health Insurance (NHI) and consisted of a cost-effectiveness analysis (CEA) of three reimbursement strategies targeting different groups of travelers which have been identified in the light of epidemiological evidence and display different risks of contracting malaria. The analysis has revealed that the reimbursement of antimalarial chemoprophylaxis would have a positive effect on malaria prevention in France. By entailing an additional cost to the NHI, the implementation of each of the three refund strategies is expected to result in a decline in imported malaria incidence in the country and in the number of annual malaria-related deaths, compared to the current strategy of no reimbursement. The incremental cost-effectiveness ratio (ICER) of the policies, expressed in terms of cost per additional malaria case averted with respect to the status-quo (absence of reimbursement), goes from € 15,136 for the most cost-effective strategy to € 34,623 for the least efficient approach.

As the three strategies refer to different population of travelers, they have been evaluated through separate CEA analyses, comparing them to three distinct status quo. For this reason, it is impossible to compare their cost-effectiveness impact, as it is done traditionally in CEA of multiple and

[97] The time required for half the amount of a substance (such as a drug, radioactive tracer, or pesticide) in or introduced into a living system or ecosystem to be eliminated or disintegrated by natural processes. Source: https://www.merriam-webster.com/dictionary/half-life

[98] Compliance (or adherence) to a treatment is the defined as the consistency and accuracy with which someone follows the regimen prescribed by a physician or other health professional.

competing strategies. Moreover, the analyses focus on reimbursement strategies and not on the drugs themselves. New preliminary results comparing costs and medical benefits of these two drugs (DOXY and ATVP) show that DOXY might represent a decrementally cost-effective intervention. Indeed, for a relatively small utility loss due the demanding nature of a treatment with DOXY compared with the much simpler administration schedule of ATVP, DOXY is much cheaper. However, when the negative externality produced by the utility loss of patients is considered - namely a lower protection from malaria due to lower adherence rates to DOXY - DOXY could be less cost-effective than expected. ATVP, which displays much higher compliance rates, could result in a much lower cost per additional malaria case prevented.

These six case studies show a variety of d-CEIs with different levels of success regarding adoption. They also illustrate the fact that the d-CEI qualification is fluctuant over time and across jurisdictions, which partly explains the difficulty in gathering comparable and robust evidence.

3.4 – Evidence on policy-makers' preferences regarding d-CEIs

A narrative literature review on policy-makers' stated preferences was carried out in task 1 by the URC-éco at AP-HP as a complement to the systematic literature review on d-CEIs. The purpose was to provide an overview of the currently available evidence on the use of stated preferences methods for eliciting, the preferences of policy-makers (see appendix A) and to validate the methodological choice of using a discrete choice experiment for the behavioral economics inquiry.

Policy-makers involved in HTAs increasingly have to balance constrained resources and an increasing demand for healthcare services. Preference-based approaches offer complementary information for priority-setting decisions and are a useful tool to support decision-making. However, while there are many patients' preference studies, there are fewer cases on the general population preferences and even fewer cases measuring preferences of policy-makers themselves. Articles were mostly found within the policy area of health, environment, transport, and food and on patient/public/consumer preferences. In these studies, what constitutes a policy-maker (or a decision-maker) is not always clear. Most often, it is specified in the article, but it varies. A decision-maker can be a consumer, user, health professional or a patient, namely someone involved in making healthcare decisions depending on the context. In health, policy-makers are more often defined as regulatory and HTA bodies. Patients' and consumers' preferences have not been included in this review.

Stated preferences

While evaluating new medical interventions, decision-makers have to balance their decisions between benefits and risks; this balance is often the focus of studies relying on preference-

elicitation methods in the literature. The methods can be used to produce formal, evidence-based evaluation of decision-makers values (Hauber, B et al., 2013). Some scholars draw a distinction between DCE and Conjoint analysis, as the term "conjoint analysis" covers any preference elicitation method (Louviere 2000; Ryan, Mandy et al. 2008). The literature retrieved was divided into two categories: direct-elicitation methods and conjoint analysis. The majority of studies used a discrete choice method (here categorized as conjoint analysis). The results show that the literature on benefits-risk preferences is extensive and growing fast.

For instance, in a study on pension plans, the authors developed tools for studying the relationship between policy-makers' preferences related to pension plans compared to those of the general population. The data retrieved from the discrete choice experiment conducted in this study allow for a better understanding of the compulsory enrolment in pension plans. The study found that policy-makers' preferences are sensitive to the framing effects (Goldin, Jacob et al. 2018).

Another direction consists in improving methods (Masatlioglu, Nakajima and Ozbay, 2012) with a view to better identify preferences of decision-makers. Authors identify three potential barriers to an accurate identification: 1) policy-makers' ability to maximise welfare, 2) policy-makers' lack of attention, 3) framing effects susceptible to influence policy-makers' responses (Masatlioglu et al., 2015).

More generally, two methods (conjoint analysis and willingness to pay) are used to investigate how decision-makers construct their preferences, make decisions and process information in healthcare. Studies tend to suggest that policy-makers are often making non-rational decisions (in the economic sense), using cognitive shortcuts (Lloyd, 2003).

Discrete choice experiment method

Paolucci et al. used a DCE within the health policy area to better inform Chinese policy-makers when implementing health strategies as well as to increase transparency. The DCE study was carried out with 78 provincial and national level policy-makers to measure their preferences on six policy attributes linked to equity and efficiency. The results of the multi-criteria decision-analysis revealed trade-offs between effectiveness and equity, where the effectiveness criteria were found to be the most important for policy-makers (Paolucci et al., 2015).

Increased knowledge and insight in policy-makers' preferences is essential since national guidelines (in addition to cost-effectiveness) often include other factors in reimbursement decisions. Weights attached to these various factors are rarely quantified. Thus, decisions can be highly dependent on decision-makers' preferences. A discrete choice experiment was carried out with 153 healthcare

professionals and policy-makers involved in the regulatory process in Austria, Hungary and Norway. The objective was to discover cross-country differences in effectiveness and equity attributes of interventions. The result of the study showed differences between the three countries, where policy-makers in Austria and Hungary were showing more effectiveness- than equity-oriented preferences. In contrast, those in Norway were showing equal preferences for equity and efficiency attributes (Baji, Petra et al. 2016).

A DCE was employed to develop a decision support system for health technology assessment in Iran. DCE, using stepwise regression, resulted in 64 scoring tools shaping the decision support system (guide) for all HTA related policies (Yazdani, Shahram et al., 2017).

It appears from the literature that little is known about the preferences of the population for pharmaceutical funding decisions. Moreover, the preferences of members of an assessment body may differ from those of the general public. A DCE has been carried out to measure the consistency of preferences between the Australian public and members of the Pharmaceutical Benefits Advisory Committee and its Economic Subcommittee. The study found that funding decisions by the committees were consistent with the choices of society (Whitty, Jennifer A et al., 2011).

One study compared the preferences of policy-makers (n=141), physicians (n=311) and patients (n=508) regarding the introduction of teleconsultations instead of in-clinic consultations in primary care in Israel. The method used was a DCE (4 attributes, 12 choice tasks of 2 labelled alternatives). A random effect logit model analysis was applied to analyse the data. Findings may inform the implementation process of new alternatives in primary care. The DCE showed differences between the trade-offs, attribute rank order and the probability of uptake for the teleconsultation (e.g. 68% in patients compared to 86% in policy-makers) (Chudner, I et al. 2019).

Best-Worst-Scaling (BWS)

The only BWS that can measure trade-offs in preference elicitation is the third version (Ryan, Mandy et al. 2008). "Case 3 best-worst scaling – that is, discrete choice experiments" (Louviere K. Jordan et al. 2015, pp. 265), in which the task consists in identifying the "worst" and the "best" alternative in each choice set. The BWS Case 3 is the version that is closest to a DCE, but with the extension allowing for best and worst choices (Cheung K.L. 2016). The minimum number of choice sets needs to be of three or more (multi-profile case). Thus, the policy-maker has to choose, not only the preferred but also the least preferred option.

In one study, binary DCE and multi-criteria BWS (Case 3) were compared when assessing healthcare programs. Bayesian efficient design was used to identify preferences for 48 EQ-5D-5 health states,

leading to 8 choice sets for the BWS model and 24 choice sets for the DCE model. Both methods were relatively easy to understand for respondents (100 participants). Still, the DCE was slightly more accessible, took less time to complete and had a higher response rate. "the intraclass correlation coefficient (ICC) of the DCE was higher than that of the BWS. The variances associated with the latent utilities estimated from the DCE were larger than those from the BWS. The DCE is more feasible and reliable than the BWS in valuing the EQ-5D-5L" (Xie, Feng et al. 2014).

The best-worst scaling method has been used to elicit preferences of joint property forest owners in the forest industry. By using BWS, the study aims to improve the forest management programs by identifying the best versus the worst preferences in regards to different management alternatives. Results show that the owners can be classified into two groups: one group prioritizing direct economic incentives and faster returns; the other group, composed of younger members, tends to prefer policies that benefit social spillovers and the environment. Authors conclude that BWS is an appropriate method for identifying decision-makers' preferences under conflicting criteria (Loureiro, Maria L, et al. 2012).

In another study, the two methods (DCE and BWS) were compared, using a survey of preferences for mobile payments. The authors "compared the mixed logit model and the latent class model using three non-nested tests. The results indicate that the mixed logit model is superior to the latent class model in all three tests". The BWS is good for consumers since it slightly lessens the cognitive burden, delivers supplementary information and demonstrates better quality (Guo, Qinxin et al., 2019).

Delphi survey

A Delphi survey has been carried out with 66 public health decision-makers in England and Wales to elicit their views on the different methodological features of economic evaluation. The study consisted of two rounds of questions; the first round allowed open-ended recommendations in addition to a 5-point Likert scale response. The final survey included 36 questions, and levels and strengths of agreement were assessed. The results revealed preferences for a flexible decision-making process and were used to inform guidelines for public health evaluation (Frew, Emma, et al. 2019).

4 - A behavioural economics inquiry

Introduction

Behavioural economics techniques such as discrete choice experiments[100] are increasingly applied to the health field, as preference elicitation (for both patients and decision-makers) becomes more central. Discrete choice experiments are used to elicit participants' stated preferences by analysing respondents' trade-offs amongst different hypothetical situations. These situations are characterised by a selection of attributes and levels intended to offer a simplified but relevant description of the stakes of complex decisions, in the sense that they necessarily involve choices. The Discrete choice experiment designed for this project aims to inquire into policy-makers willingness to adopt (or not) d-CEIs. To make reimbursement recommendations, additional information is needed on whether decision-makers are prepared to consider these interventions in the healthcare basket and, if so, to analyse the main determinants of their willingness to adopt these interventions beyond cost-effectiveness, such as reversibility of the decision or level of uncertainty on the expected financial gains, etc.). The following sections present respectively the DCE research hypotheses and design, the DCE econometric results and the DCE qualitative analyses.

4.1 - DCE research hypotheses and design

The design of a discrete choice experiment for the analysis of decision-makers willingness to consider, and possibly adopt, d-CEIs has been informed by a number of preliminary steps. The first is a systematic international literature review (see Appendix A), which identified the existing level and quality of evidence on d-CEIs and their potential associated savings. A narrative review of existing HTA bodies adoption of d-CEIs further documented attitudes and obstacles to adoption. Qualitative interviews were also carried out in order to inform the design of the experiment and the choice of attributes and levels.

[100] Jacquemet, Nicolas and l'Haridon, Olivier (2019). *Experimental Economics: Method and Applications*, Cambridge: Cambridge University Press, 450 pages, ISBN 978-110762977-6

4.1.1 - Experimental design

The discrete choice experiment was kept generic, with no reference to specific interventions or illnesses, in order to avoid strong anchoring effects, as recommended in the behavioural economics literature.

Another distinguishing feature is the fact that respondents were asked to act as a policy officer in charge of a regional budget. This role playing was meant to minimize the hypothetical bias and the difficulty encountered by respondents in the pilot phases to acknowledge the existence of limited resources and therefore the need to make such trade-offs.

The risk of incomplete or no-response was minimized by defining an "escape" route early on in the experiment to ensure that respondents would answer a minimal set of questions even if they refused to enter the experiment itself (see figure 4.1). A specific question enabled documenting such no response cases by distinguishing whether respondents objected to the duration of the experiment, to the experimental design or to the actual focus of the study, i.e. CEIs.

Based on findings from the ethical inquiry**, a two-stage decision-making process was defined to enable distinguishing between 1) willingness to consider and 2) willingness to adopt**. As a result, for each choice-set, respondents had to first select one option between two d-CEIs; they were subsequently asked whether they would be ready to adopt the chosen d-CEI which would then replace the existing treatment (usual care)[101].

An online questionnaire was designed using Qualtrics software, targeting EU respondents from Health technology assessment (HTA) agencies or health technologies' pricing and reimbursement committees, officers of governmental or non-governmental organisations, representatives of citizens or consumer/patient advocacy groups, and health economics students.

101 "Would you be ready to substitute usual care by the option you selected?"

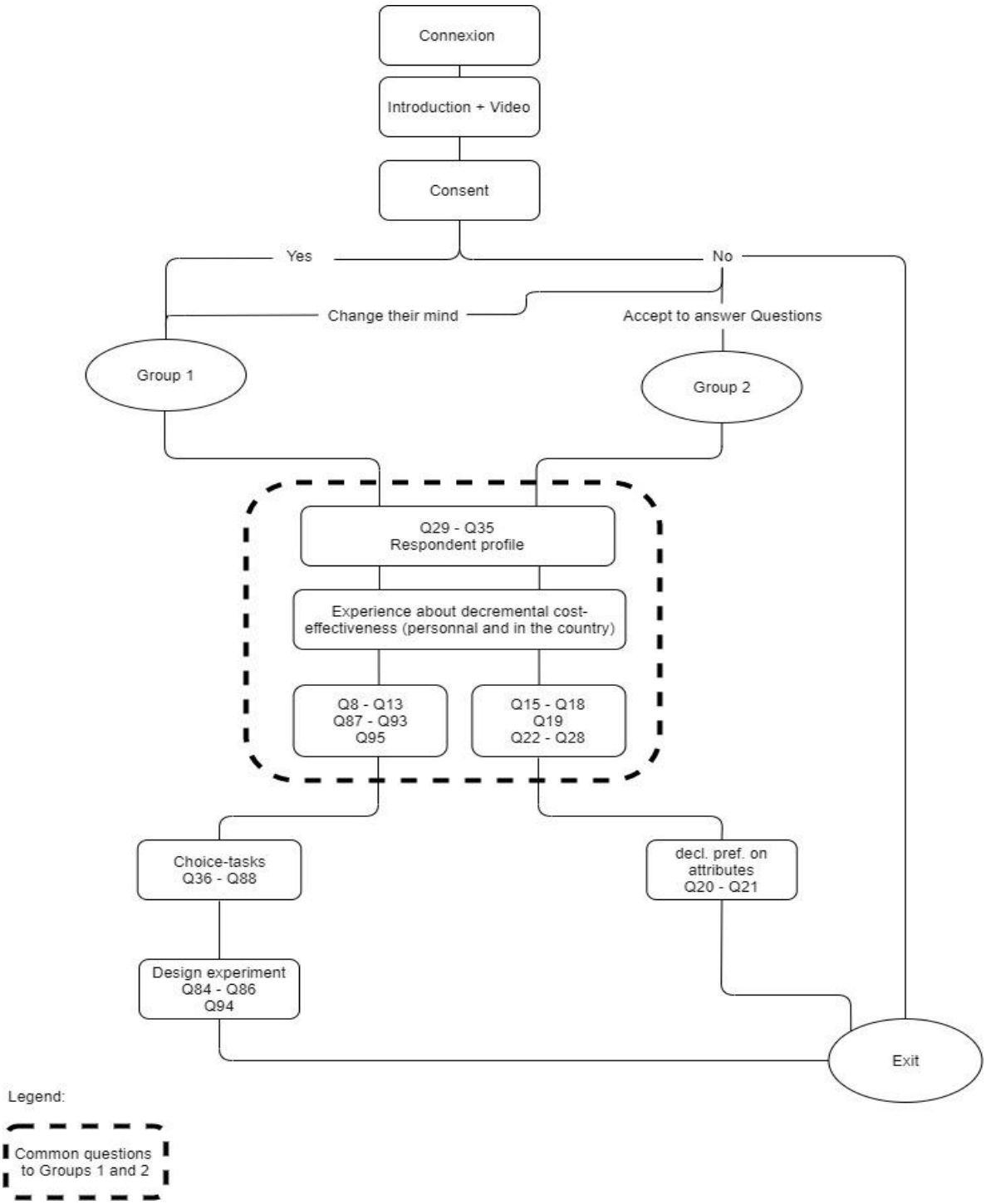


Figure 4.1: DCE structure

Source: authors' own output

4.1.2 - Choice of attributes and Levels

The experiment consisted of asking respondents to choose between two d-CEIs. For policy-makers, such a decision involves complex trade-offs between health losses and the savings generated by substituting usual care to decremental cost-effective interventions.

A large number of attributes were identified in the first stage (see table 1) and choices were made to narrow them down to a manageable size, in terms of length of time for respondents. Such a simplification of the choice environment is also necessary to allow a quantitative analysis of the experiment's data. The experiment therefore focused on those attributes which would be most relevant to decision-makers in their quest to document society's willingness to consider the clinical losses as equivalent to the cost savings, as suggested in the EunetHTA guidance.

Table 4.1 – Early selection of attributes and levels

Attributes	levels – (different options)		
Severity of disease	**The severity of health at the time of intervention**: Mild, moderate, severe, very severe.	**The gain in health (expressed in QALY):** [0; -0.009] (non-inferiority), [-0.01; -0.2] (small loss), [-0.3; -0.8] (large loss)	
Uncertainity attribute	**Quality of evidence**: RCT, mixed methods (RCT + modelling), modelling, observational study	**The probability of an intervention to be efficient**: 80%/70%/55%	
Cost attribute	**Negative cost-effectiveness ratio of the alternative**: -50K € , QALY, -200K € , QALY, -1M € , QALY	**Negative budgetary impact of the alternative:** -1,000,000 €, -10,000,000 €, -100,000,000 €	**Expected reduction in treatment cost (full treatment)**: -1,000 €, -10,000 €, -100,000 €
Population attribute	**Size of population:** 500 patients, 9.000 patients, 50.000 patients	**Type of pathology:** common disease, rare disease, orphan disease	**Age of population**: pediatric population, adult population, elderly population
Process attribute	**Patient acceptability**: preferred treatment, neutral attitude, rejected treatment, unknown	**The reversibility of the intervention:** Reversible, irreversible	

Another consideration in choosing attributes is ensuring that none will dominate the others. Based on feedback from qualitative interviews and pilots, the choice was therefore made to leave out uncertainty with respect to clinical losses as it appeared as a potentially dominant attribute.

In the final version of the experiment, respondents were asked to make trade-offs in 8 choice sets combining 3 attributes of 3 levels each. The choice-sets are constructed with three central attributes: 1) health loss, as perceived by the patient population; 2) possibility to switch back from the d-CEI to usual care, expressed in time; 3) cost-savings, expressed in a percentage of a fixed budget).

Regarding levels, a choice was made to adopt low levels of health losses in order to ensure respondents' participation. This is also in-keeping with the objective of selecting attributes and levels as close as possible to situations in which policy-makers will be most likely to consider d-CEIs. Indeed, high health losses would not be acceptable to them as they are acting on behalf of society.

Two additional attributes were introduced as sensitivity attributes by asking respondents whether they would reconsider their choice of adopting the d-CEI in case disease severity or uncertainty about the cost-savings were to increase. While these two additional attributes do not have weights attached to them, compared to the three chosen attributes, this sensitivity analysis allows capturing their potential impact on changes in decision-makers' willingness to adopt the chosen option.

Table 4.2. Discrete choice experiment: attributes and levels

Central attribute	Description	Levels
Health loss	Health loss refers to a loss in quality of life as perceived by the patient population. This could take the form of side effects, such as coughing and/or additional constraints, associated with taking the treatment (e.g. a pill every day rather than every week).	Very small
		Small
		Significant
Possibility to switch back	Possibility to switch back from decremental cost-effective intervention to usual care (expressed in time)	Possible at anytime
		Possible after some delay
		Hardly possible due to long delays
Cost-savings	Annual savings being made when switching from usual care to a decremental cost-effective intervention. The savings are defined as a percentage of a fixed healthcare budget to €100 million per year.	5%
		10%
		15%
Sensitivity attributes		
Disease severity	The disease severity attribute relates to the patient experience of the disease, as indicated by their EQ-5D Quality of Life Score.	Low
		Moderate

Uncertainty	The uncertainty attribute is based on the probability of observing the expected cost-savings if adopting the decremental cost-effective intervention.	Low
		High

We used a pairwise DCE design, a format that asked respondents to repeatedly choose which scenario would be most acceptable between two hypothetical scenarios. The content of scenarios (optimal combinations of attributes' level) was selected using an efficient fractional design using NGENE software (Choice metrics). Prior values for the preferences parameters corresponding to the three attributes were defined, with negative prior values for levels 2 and 3 of the health loss and reversibility attributes, and positive values for the levels 2 and 3 of the cost savings attributes (see **Table 4.1** for levels description). A total of 8 pairwise tasks were necessary to estimate all effects. Except two tasks (with follow-up questions) which were always placed at position 2 and 7, the order of all the choice tasks varied for each respondent (**Table 4.2** shows the content of all 8 tasks, together with choice statistics).

Table 4.3. Definition of attributes and levels

Attributes	Level	Level description
Health loss	**1**	Very small
	2	Small
	3	Significant
Reversibility	**1**	Possible, anytime
	2	Possible, with delay
	3	Hardly possible, due to long delays
Cost savings	**3**	15%
	2	10%
	1	5%

Legend

Level assumed to have positive effect on choices
Level assumed to have negative effect on choices
Level assumed to have most negative effect on choices

Table 4.4. Description of the choice tasks and frequency of choices

	Scenario 1			Scenario 2			Choice statistics	
Choice task	Health loss	Reversibility	Savings	Health loss	Reversibility	Savings	choices (N)	Scenario 1 chosen*
1	Small	Possible, anytime	10%	Very small	Hardly possible	10%	170	77%
2	Very small	Hardly possible	5%	Significant	Possible, anytime	15%	156	56%
3	Significant	Possible, anytime	5%	Very small	Possible, delays	10%	157	5%
4	Small	Possible, delays	10%	Very small	Possible, anytime	10%	161	7%
5	Significant	Possible, delays	15%	Small	Possible, anytime	5%	157	15%
6	Small	Hardly possible	15%	Significant	Possible, anytime	5%	160	82%
7	Very small	Possible, delays	5%	Very small	Hardly possible	15%	157	68%
8	Significant	Hardly possible	10%	Small	Possible, delays	15%	130	3%

* Percentage of the sample selecting scenario 1 as preferred

4.1.3 - Research hypotheses

Three empirical hypotheses motivated the design of the experiment:

1. Respondents will give priority either to the attribute on the health loss (as perceived by the patient population) or to the possibility to switch back to usual care (expressed in time) and cost-savings will be considered secondary (least important of the attributes). Expected savings will gain importance if they are high.
2. Respondents will be more willing to adopt interventions if the health loss (as perceived by the patient population) is low and if the possibility to switch back to usual care (expressed in time) is possible, at any time.
3. Respondents will be more likely to consider adoption if the two sensitivity attributes (disease severity and uncertainty of expected savings) are low, with more importance placed on the former.

4.2 – Econometric analysis of DCE

The data analysis and results consist of two parts, one qualitative and one quantitative.

4.2.1 – Effect of attributes on choices

The choice data were analysed within a random utility maximization framework i.e., assuming a random utility function for each hypothetical scenario (including a systematic and unobserved portion of utility) and assuming utility maximization decision rule (McFadden, 1974). We used a mixed multinomial logit (**MIXL**) model specification, allowing the preference parameters to be randomly distributed across the sample and thus accounting for (i) unobserved preference heterogeneity and (ii) correlation of choices between participants (McFadden and Train, 2000). The main utility function was specified as follow:

$$\begin{cases} U_{njt} = \beta_{1,n} Healthloss\_small_j + \beta_{2,n} Healthloss\_vsmall_j + \beta_{3,n} Reversibility\_delay_j \\ \qquad + \beta_{4,n} Reversibility\_hardlypossible_j + \beta_{5n} Savings_j + \varepsilon_{njt} \end{cases}$$

where U_{njt} is the utility decision maker *n* derives from choosing alternative (scenario) *j* in choice situation *t*, $Healthloss\_small_j$,…, $Reversibility\_hardlypossible_j$ represent dummy coded attributes' levels displayed in scenario *j* (level 1 of all attributes was used as reference), $Savings_j$ represent the level of savings (5%, 10%, 15%) in scenario *j*, $\beta_{1,n}, \ldots, \beta_{5,n}$ are the respective random effects (part-worth utilities) associated with each attribute level, the subscript *n* denoting respondent-specific parameters. Finally, ε_{njt} is the error term assumed extreme value type 1 distributed, thus leading to the multinomial logit choice specification (McFadden, 1974).

We estimated a MIXL (using 500 Halton draws) with correlated random coefficients between all 5 attributes' levels, assuming normal distribution for each parameter $\beta_{k,n}$. Though computationally intensive, this model is known to be most flexible (Hess and Train, 2017). In particular, it allows accounting for scale heterogeneity, i.e., various degrees of consistency of decisions across respondents (Hess and Rose, 2012).

In order to visually represent the degree of preference heterogeneity, we predicted individual-level coefficients from the MIXL model (i.e. $\hat{\beta}_{k,n}$, $k = 1, \dots ,5$) using the methodology detailed in (Revelt and Train, 1998).

4.2.2 – Effect of attributes on willingness to adopt d-CEIs

We analysed the impact of each attribute on the willingness to substitute usual care using random effects linear probability model, with the response to the question "*would you be willing to substitute usual care by the option you selected?*" as the dependent variable, and the attributes of the selected option as independent (exogenous) variables. Note that because of the experimental design (exogeneity), the results of these models are not significantly different from a fixed effects specification.

Preference estimates

Descriptive statistics on frequency of choices for each task (**Table 4.2**) shows that there are large variations in the propensity to choose either scenario 1 or 2, from as little as 3% of the sample selecting scenario 1 in task 8 (considered as dominant), to 82% selecting scenario 1 in task 6. Task 2 was more balanced with 56% selecting scenario 1.

In mixed logit models with correlated random coefficients, four attributes' levels had negative and statistically significant part-worth utilities, in line with a priori expectation (**Table 4.3**): small health losses (β=-2,39), significant health losses (β=-8.1), reversibility possible with delays (β=-2.1), reversibility hardly possible due to long delays (β=-4.2). In other words, all other measures being equal, respondents' likelihood to choose one scenario over the other decreased with these attributes' levels (relatively to the reference). On the contrary, the level cost savings had positive and significant impact on choices: every 5% savings from fixed budget increased utility by 1.6. We tested the robustness of our results to deviations of the linearity assumption for the cost-savings attributes, but the results did not favour more complex (e.g., categorical or polynomial) specifications in terms of model performance (see **Appendix B**). These preliminary results do not support a priori the assumption of marginally decreasing valuation of benefits.

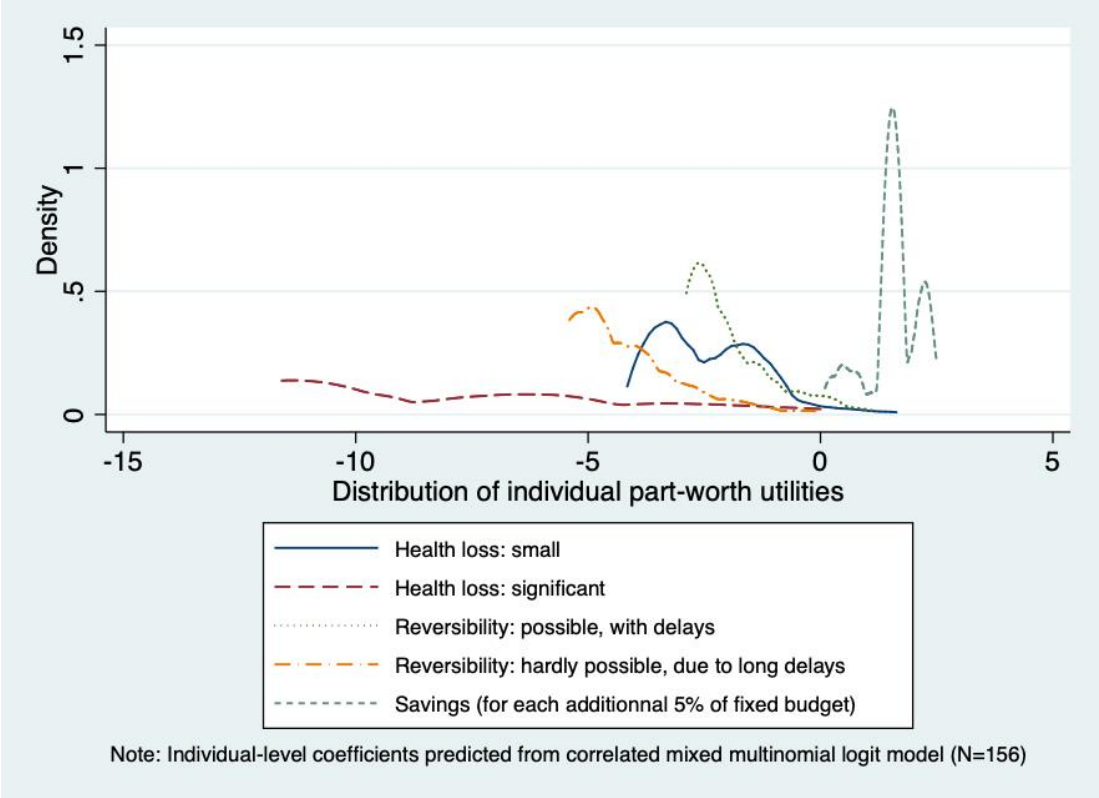
Significant preference heterogeneity was found for three attributes' levels (the two health loss levels, and the level "possible with delay" of the reversibility attributes), with statistically significant standard deviations of the underlying normal random effects (**Table 4.3**). Graphical distribution of the predicted individual level coefficients (β_n) confirms significant heterogeneity in preferences for the above-mentioned attributes' levels (see **Figure 1**).

Table 4.5. Results of the MIXL model (N=156) – correlated random coefficients

Dependent variable: choice between scenario 1 or 2	**Mean**		**SD**	
	Est	Std. Err	Est	Std Err.
Health loss: very small	*Ref*		*Ref*	
Health loss: small	-2.397***	(0.461)	1.437***	(0.370)
Health loss: significant	-8.079***	(1.215)	2.323***	(0.579)
Reversibility: possible, at any time	*Ref*		*Ref*	
Reversibility: possible, with delay	-2.056***	(0.577)	1.065**	(0.448)
Reversibility: hardly possible, due to long delays	-4.244***	(0.559)	0.251	(0.654)
Savings (linear, per 5% of budget)	1.577***	(0.324)	0.472	(0.351)
N (individuals)	156			
Choice observations	1,222			
Log-likelihood	-451.06			

Note. The estimates are interpreted as average part-worth utilities: they represent the average effect of the attribute on the underlying utility.
Statistical significance: ***: 1% **: 5%; *: 1%

Figure 4.2. Distribution of individual-level coefficients derived from correlated MIXL model



Note: Individual-level coefficients predicted from correlated mixed multinomial logit model (N=156)

This figure displays the distribution of individual-level preference parameters for each attribute (level) relative to the reference (for categorical attributes).

Compensating variation

From these results (average estimates), we estimated that decision makers would be willing to accept d-CER interventions leading to "small" (vs. "very small") health losses only if it was compensated by savings of 7.6% of the fixed budget, "significant" (vs. "very small") health losses only if it was compensated by savings of 25.6% of the fixed budget, possible reversibility with delays (vs. "possible at any time") only if it was compensated by savings of 6,5% of the fixed budget, and hardly possible reversibility due to long delays (vs. "possible at any time") only if it was compensated by savings of 13.5% of the fixed budget.

4.2.3 - Determinants of willingness to substitute usual care

Overall, there was relatively high willingness to substitute usual care with the selected hypothetical option, from a minimum of 62% in task 2, to a maximum of 94% in task 4 (**Table 4)**. Note, however, that this willingness decreased significantly in the following scenarios:

- Disease severity of the patient changed to moderate: the willingness to substitute decreased from 62% to 40% in task 2, and from 80% to 51% in task 7.

- Uncertainty related to cost-savings changed to high: the willingness to substitute decreased from 62% to 24% in task 2, and from 80% to 27% in task 7.

These results show that uncertainty related to cost-savings is extremely important for ensuring willingness to adopt d-CER interventions.

The analyses were also stratified according to the responses to the questions: "would you be willing to adopt d-CER interventions is savings were reallocated to": (i) "patients targeted by the decrementally cost-effective intervention?"; (ii) "patients across disease areas?" ; (iii) "to the general population, for interventions outside healthcare (e.g. education)?" (yes / not sure /no)

We regrouped respondents who responded either "not sure or no" in all three questions, and replicated the analyses on this subgroup (N=30). As expected, we found that, in this subgroup, willingness to substitute usual care with the selected hypothetical option was significantly lower in all choice tasks, from a minimum of 33% of acceptance in tasks 2 and 7, and a maximum of 73% acceptance in task 4. Besides, the willingness to substitute if either (i) disease severity changed to moderate or (ii) uncertainty related to cost-savings changed to high, were also lower compared to the entire sample.

The willingness to substitute usual care also varied according to the attributes of the d-CER interventions (**Table 4.5**). Results of random effects linear probability models on the sample of chosen scenarios reveal that the willingness to substitute usual care decreased by 11.2 percentage points (pp) if health loss was small, decreased by 24.7 pp if health loss was significant, decreased by 9.7 pp if reversibility was possible but with delay, decreased by 30.9 pp if reversibility was hardly possible due to long delays, and increased by 8.8 pp for each additional 5% savings of fixed budget. These results show that reversibility appears as important as health losses in willingness to adopt d-CER interventions.

Table 4.6. Descriptive statistics on the follow-up question: willingness to substitute with usual care

	Overall (N=156)			Not sure / not willing to adopt d-CER intervention (N=30)		
	Willingness to substitute usual care with the selected option if			*Willingness to substitute usual care with the selected option if*		
Choice task	Low disease severity and low uncertainty (%)	Disease severity of the patient changes to moderate (%)	Uncertainty related to cost-savings changes to high (%)	Low disease severity and low uncertainty (%)	Disease severity of the patient changes to moderate (%)	Uncertainty related to cost-savings changes to high (%)
1	87%	-	-	53%	-	-
2	62%	40%	24%	33%	26%	33%
3	88%	-	-	60%	-	-
4	94%	-	-	73%	-	-
5	76%	-	-	46%	-	-
6	62%	-	-	40%	-	-
7	80%	51%	27%	33%	25%	19%
8	79%	-	-	46%	-	-

Table 4.7. Attributes' impact on the willingness to substitute usual care. Results of random effects model

	RE model	
	Est	Std. Err
Health loss: very small	*Ref*	
Health loss: small	-0.112***	(0.024)
Health loss: significant	-0.247***	(0.040)
Reversibility: possible, at any time	*Ref*	
Reversibility: possible, with delay	-0.097***	(0.025)
Reversibility: hardly possible, due to long delays	-0.309***	(0.027)
Savings (linear, per 5% of budget)	0.082***	(0.015)
N (individuals)	156	
Choice observations	1,222	

Note. The estimates are interpreted as marginal effects one the probability to "be willing to substitute". For instance, small health losses decreases the probability to be willing to substitute the scenario with usual care by 11.2 percentage points.
Statistical significance: ***: 1% **: 5%; *: 1%

4.3 - Qualitative analysis of the DCE

At the outset of designing the Discrete Choice Experiment (DCE), three preliminary semi-structured interviews have been conducted with policymakers to help inform the choice of attributes and levels. A full report on the method and summary has been provided in MS43. These preliminary results are in line with some important points that the DCE results have corroborated. In their feedback, the policymakers first addressed remarks about the importance of patient preferences when trading-off cost- and outcomes- reductions; they especially emphasized the need to share with the patients clear information about the reversibility of the treatment offered. One participant mentioned that considering irreversible d-CEIs is very unlikely. They mentioned that there is a need to clarify the nature of the disease severity and that health technology assessments should be based on multiple criteria, which is not fully the case currently. They also pointed out a lack of transparency in health technology assessments, especially related to prices, and in resource allocation, along with the fact that doctors are often unaware about the cost-effectiveness of the medicines they are prescribing. Regarding the costs, they pointed out that the public discussion in France is not mature and well informed when it comes to the sustainability of public expenses. Finally, they hypothesized that adoption of a decremental cost-effective intervention would certainly be driven by the amount of money that can be saved.

These preliminary interviews have been completed in a first piloting phase of the discrete choice experiment (DCE), by conducting a qualitative analysis on seven individual think-aloud sessions with policymakers and health economists while they were completing the DCE. The interviews were recorded for clarification purposes. As in the preliminary interviews and consistent with results of the DCE, decision-makers expressed a need for additional information to make trade-offs between the attributes, with a special emphasis on the aim of the reallocation of savings.

After the analysis of the results, there is more information on the relative importance of the selected attributes. Significant health loss appears problematic and would be rejected by some respondents. Some respondents underlined that patients might experience delays differently and a respondent did question whether the possibility to switch back to usual care might contradict the decremental cost-effectiveness approach, by reducing the prospects of cost-savings. According to the uncertainty about expected savings, many respondents suggested that it would be helpful to specify confidence intervals because this would ease how this uncertainty can be dealt with in the process of deciding.

One respondent stated that he would heavily hesitate to adopt a d-CEI intervention surrounded with a high uncertainty on the cost-savings since cost-savings are a major reason why considering a d-CEI. Disease severity was perceived as an important attribute, which was expected, while the importance placed on cost-savings and the prospect of balancing reversibility with cost-savings were both more important in the open comments accrued by participants.

4.3.1 Method

The following qualitative analysis explores the open comments that respondents to the Discrete Choice Experiments (DCE) left in the open-text boxes. A vertical analysis has been conducted in order to extract from the comments of each participant the relevant qualitative inputs under pre-identified DCE hypotheses and a number of set themes chosen for the political economy report (PER). A horizontal analysis was subsequently conducted to triangle the inputs from different respondents in order to offer a synthesis of the results for each of the hypotheses and themes. Five hypotheses guided the design of the DCE; 9 themes were identified in the construct of the PER. Each hypothesis is addressed below; only 7 themes are detailed to avoid redundant information in the report of the results. The analysis has been conducted using the qualitative analysis software MAXQDA2020 to ensure traceability.

In the following qualitative analysis, “respondents” is understood as those who made a qualitative input among the total number of participants in the DCE (136, which is the number of questionnaires have been analysed at this stage). For each hypothesis/theme, the number of respondents is systematically reported. For readability, the following scale is used when reporting the results: percentages refer to the number of open comments from respondents who provided inputs fitting in the corresponding theme:

0 – 20%	**20 – 40%**	**40 – 50%**	**50 – 75%**	**75 – 100%**
“a few”	“some”	“nearly a half”	“the majority”	“most”

4.3.2 - Qualitative analysis of DCE hypotheses

H1. Respondents will give priority either to the attribute on health loss (as perceived by the patient population) or to the possibility to switch back to usual care (expressed in time); cost-savings will be considered secondary (the least important of the three considered attributes). Expected savings will gain importance if they are high. (n=87/136)

A majority of the respondents declared giving priority to the attribute of health loss and emphasized healthcare professionals' obligation of means and the role of trust in the relationship between them and their patients. The importance placed respectively on reversibility and cost-savings was comparable: those who highlighted the importance of reversibility justified it by the fact that it may enhance patients' acceptability, due to the possibility to switch back to usual care if the quality loss they experience is found to be unacceptable (emphasis on the individual perspective); those who highlighted the importance of paying attention to cost-savings justified it by the fact that it contributes to the maximization of population health and of an actual reallocation in priority areas (emphasis on the collective perspective). Worth noting, respondents who considered cost-savings did so in relation to reversibility or health loss attributes; these two latter attributes were only rarely considered *per se*. The relationship between cost-savings and other attributes, especially health losses, varies depending on how the question is framed. When asked to rank the three attributes, respondents ranked cost-savings third (health loss ranking first). However, when deciding whether to adopt the chosen d-CEI option, the cost-savings attribute was the most often quoted in the open comments as a reason for adoption.

H2. Respondents will be more willing to adopt interventions if the health loss (as perceived by the patient population) is low and if the possibility to switch back to usual care (expressed in time) is possible, at any time. (n=70/136)

When choosing between two d-CEIs in the choice sets, respondents declared focusing on the level of the health loss attribute before considering reversibility and cost-savings. The option with a significant health loss was perceived as hardly "*acceptable*" regardless of the other attributes. If health loss was "very small" and "small" in both d-CEIs, respondents did not systematically choose the d-CEI with the "very small" level of health loss but considered the reversibility and the cost-savings: cost-savings gained importance as the level increased (15%) and, in their comments, respondents reported cost-savings as a reason for adoption (when reversibility could be perceived as secondary). Furthermore, a few participants pointed out a possible conflict between cost-savings

and reversibility: a high reversibility might reduce the prospects of cost-savings since patients would probably switch back to usual care.

When turning to the adoption question, respondents declared paying attention to health loss and reversibility. When health loss was small in the choice sets, most participants agreed to adoption, based on the prospect of improving population health with little harm for the patient. More surprisingly, a high level of cost savings (15%) did counterbalance longer delays to switch-back to usual care (reversibility) or, although it was mentioned only in a few open-comments, a significant health loss. For example, in a choice-set with the prospect of a small health loss and of 15% savings, participants were more likely to adopt the intervention, justifying their choice with the high collective gains in comparison to the small health loss. Here, reversibility was not reported as a relevant choice criterion. When balancing cost-savings and the uncertainty sensitivity attribute, the higher the cost savings, the more respondents were ready to accept a higher uncertainty, as collective benefits seemed to be worth the risk.

Hence, the hypothesis seems partially confirmed: health loss and reversibility are important when choosing to adopt a d-CEI but cost-savings seem play a greater role than expected; conversely, reversibility might play a lesser role, if anything because a greater reversibility might actually reduce the value of substituting.

H3. Respondents will be more likely to consider adoption if the levels of the two sensitivity attributes (disease severity and uncertainty of expected savings) are low, with more importance placed on the former. (n=48/136)

A majority of respondents reported being more willing to adopt d-CEIs if the levels of the sensitivity attributes (disease severity and uncertainty about cost-savings) are low. However, it is worth noting that the two attributes are equally quoted in the open comments. This suggests that the prospects of cost-savings may be of a higher importance than expected. The reason can be that cost-savings condition the value of adopting d-CEIs, as respondents would not be willing to accept health losses for little gain. It was also mentioned that, in the case of a high uncertainty on cost-savings, there was a risk for a d-CEI to imply additional costs, instead of savings (adopting a new intervention being burdensome, whether time- or resource-consuming). For a few of the respondents, a higher level of uncertainty in the cost-savings was held acceptable only in regard of a high rate of expected cost-savings (15%).

A majority of respondents still mentioned disease severity as being more important than uncertainty about cost-savings. This attribute was reported to vary with health loss, the lower the disease severity, the more acceptable a health loss (whether "very small" or "small"). Half of respondents mentioned that they would not feel comfortable substituting if the disease severity were higher than the low level, as it would imply a higher health risk. Some respondents, however, considered that a moderate disease severity can be justified if precise information were available about the health states losses at stake.

The hypothesis is therefore partially confirmed: higher disease severity or uncertainty about cost-savings reduces respondents' willingness to adopt the d-CEI chosen in the first stage. However, some participants were ready to adopt even after an increase in disease severity (from low to moderate (only one respondent held disease severity as not being relevant in the adoption decision). By contrast, an increase in uncertainty about cost-savings led most respondents to reject adoption, for the d-CEI they had chosen lost value.

H4. The prospect of accepting a reduction of effectiveness seems suspicious ("unethical") in healthcare. (n=14) AND H5. The political sensitivity of d-CEIs may be related to the fact that it seems to place the different actors involved in role-conflicts (double-agency) or at least to the fact that it puts emphasis on the dual roles anyone plays in the healthcare system. (n=10)

Few respondents informed hypotheses 4 and 5 which address the ethical and political sensitivity of d-CEIs. Some respondents mentioned difficulty with what they perceived as acting against health, held as a good and as a right to individuals. They wondered about the morality of what they perceived as an equivalent to "*sacrifice the few for the many*". They also reported difficulties to accommodate the twin goals of privileging collective interests and of preserving a trust-based relationship between doctors and patients; a few respondents wondered about the legality to switch current care for an intervention that reduces health outcomes. Some respondents mentioned that the choice-tasks in the DCE caused them to feel bound to make "*concessions*" because of healthcare budget constraints. For nearly half of respondents, the Covid-19 crisis revealed that budget constraints might actually be waived, since money could be found as per needed. However, some respondents held the view that patients cannot be offered the full range of treatments "whatever their costs, [which] is an awful principle"; in that sense, they considered d-CEIs as a form of solidarity. For these respondents, the Covid-19 crisis improved public awareness and acceptability of cost-savings in healthcare, making it potentially less politically sensitive to opt for d-CEIs; they held

such concessions as "*acceptable*" under the provision that the necessity to make savings, as well as their destination, are well-documented and can be made transparent to individuals, as well as information on comparators and alternative treatments.

4.3.3 - Qualitative analysis of selected themes

Cost-reduction. References to the objective of reducing costs in healthcare. (n=23/136)

Only a few respondents rejected the goal of reducing healthcare costs. Some respondents highlighted the discrepancy, in their view, between economic methods and the practice in healthcare. According to them, in such setting, clinical effectiveness should be the only criterion to consider.

Healthcare basket. References to the role or importance of cost-effectiveness in the provision of healthcare goods and services. (n=8/136)

Half of the respondents acknowledged in open comments the importance of cost-effectiveness as an evidence-basis to healthcare basket definition. Some respondents noted that this approach is instrumental to two ends: population health and patient safety; in this view, one comment sees d-CEIs as an opportunity to generate additional information on which areas should benefit from the reallocation of savings. Nearly half of respondents also highlighted that scarcity and increasing healthcare expenditure are now part of the public debate; a few called for monitoring variations in patients' responses to substituting d-CEI for usual case, in order to identify sub-groups for whom an intervention might no longer be cost-effective.

Willingness to adopt d-CEIs. References to the role or importance of preferences regarding the "slope divide". (n=60/136)

Willingness to pay and willingness to adopt were discussed by some respondents. For respondents declaring their willingness to pay for a health gain, the most important factors were quality of life and an intrinsic value of health that should be kept independent of cost considerations. For those addressing their willingness to accept a health loss for a cost-saving, the argument was made that reversibility can be viewed as a margin of choice, as a guarantee for patient security, or as a risk-ceiling. A few held the view that patients' preferences should be accounted for, for instance risk aversion or willingness to suffer a health loss.

State interferences. References to the limits of State action when regulating the healthcare system. (n=79/136)

Most respondents acknowledged the State's competence to interfere with individual rights, but they also pointed out the need to justify it on evidence-based criteria, namely as per mentioned: disease severity of the targeted population, health loss compared to usual care, side-effects, reallocation of savings. Disease severity and savings' reallocation ranked high in this list of candidate criteria: State intervention in favour of d-CEIs may gain social acceptability if it concerns low or moderate disease severity, or if it is clearly tied to well-specified State responsibilities regarding population health. A general condition for State intervention to be acceptable is transparency to the general population on the evidence-base for d-CEIs, thereby raising awareness of their existence. Reallocation of savings (including beyond the population targeted by the d-CEI) was considered as a means to reduce inequalities and was deemed key to increasing social acceptability; different domains were mentioned beyond healthcare, such as prevention or education. Perceptions of the effects of the Covid-19 crisis remained equivocal: on the one hand, it was considered to increase social acceptability because it made scarcity, budget constraints, and the need for solidarity more tangible; on the other hand, it may have eroded people's willingness to accept State intervention or the existence of inefficiencies in the healthcare system ("suboptimal care").

Quality, equity, or sustainability of the healthcare system. References to general principles or values mentioned when discussing fairness, cost-effectiveness or resource allocation. (n=27/136)

The most often quoted value was equity and the need for social justice. For instance, when asked which other attributes would need consideration when deciding to adopt a d-CEI, some respondents suggested: the social status of the targeted population, the acceptability of the intervention in this population, gross domestic product (GDP) of the country, and health inequalities in the country. A few respondents from different countries mentioned different core values of healthcare systems: in France, equity and solidarity; in the US, quality and individual welfare.

Institutional designs. References to the involvement of stakeholders in the decision to adopt cost-effective health technologies. (n=84/136)

Most of the respondents reported no difficulty in acting as a local health officer in charge of a patient population and to translate this role in their country settings (only a few highlighted the difficulty to find a similar role because of a high level of centralization). For a few participants, being an elected health officer could make a difference, the choice to consider d-CEIs was harder in this

case compared to settings where decisions are made by centralized or bureaucratic instances. A few respondents mentioned the importance of improving training for decision-makers on cost-effectiveness approaches. A few also insisted on the role of patient associations in highlighting the relationship between cost-effectiveness and patient-centred considerations. Finally, some participants underlined that it was likely that if 'local health officers' might be in charge of adopting d-CEIs, they would have no control on the reallocation of savings.

HTA methods. References to the role and importance of health technologies assessment in the decision to adopt d-CEIs. (n=10/136)

Nearly half of respondents highlighted the role of HTA when considering d-CEIs as well as its relevance to "*all health providers*". HTA can provide the evidence-base that is necessary to that end. For one respondent, if based on sound evaluation, patient preferences do not necessarily have to come into play, as security is already warranted.

4.3.4 – Qualitative analysis of workshop feedback

A workshop was conducted on April 3rd, 2021 with 16 French decision-makers including members from the French social insurance fund, the Economic and Public Health Assessment Committee (CEESP) from national Authority for Health (HAS), the French Pricing Committee (CEPS), and researchers in health economics, public health and political sciences. All participants had completed the discrete-choice experiment before the workshop. The objectives of the workshop were to discuss the methods of the Discrete Choice Experiment, the preliminary results of the experiment, the concrete illustrations of d-CEIs (since the experiment was generic), widening the field of application by giving examples of non-pharmaceutical interventions (vaccines, physical activity). The following qualitative analysis is based on extracted excerpts from the transcript of the workshop. A de-identification has been carried out and a number has been assigned to each participant (P1, P2…) in the transcript and in the following results. The analysis has been conducted by two researchers who performed a double coding of the excerpts[102].

[102] An adjudication meeting has been then conducted on 22.03.21 in order to mitigate discrepancies.

4.4.1 – Qualitative analysis of the workshop transcript

Importance and levels of attributes

The relative importance and the levels of the health loss, cost-savings and reversibility attributes have been discussed by three participants. P1 highlighted the importance of the reversibility attribute paired with the disease severity for stakeholders to accept a d-CEI. The reversibility could influence the decision in scenarios where the disease severity is set at the same level. Such factors could also be introduced in order to explain the changes in variation in the slope of the ICER in the N-E versus S-W quadrants instead of referring to the Tversky and Kahneman prospect theory. The individual and subjective attitudes and preferences towards the probabilities may be too unstable to explain the making of public decisions. A criterion which could be used is a reversibility rate justifying a limitation of individual freedom of choice. P2 noticed that the disease severity can modify the meaning of "reversibility", highlighting that different scenarios of reversibility should be studied according to the type and the severity of the disease. P4 underlined the attribute of cost-savings through the concept of scarcity on the targeted resources. What justifies the decrementally cost-effective approach understood as a decrement in effectiveness is the level of the expected gains: this should be accounted for when the gains for society can be high, based on the expected cost-savings. In that sense, decrementally cost-effective strategies should be considered for "*large markets*" (such as generic drugs).

Cost-effectiveness in healthcare

P2 mentioned an ambiguity between the evaluation of healthcare outcomes from a clinical perspective, based on the clinical effectiveness, and the fact that healthcare professionals are working in resource-limited settings (such as working-time)[103]: These limited resources imply choices based on a cost-effectiveness approach which healthcare professionals have to make in an implicit

[103] In French: « *De mon expérience à la fois de médecin ou de décideur, j'ai l'impression qu'on est souvent confronté à ça, en tout cas dans des décisions … il y a une espèce de tabou qui dit qu'on ne le fait pas mais en fait on le fait quand même assez souvent*".

way at the micro-level[104] and the meso level[105]. However, P5 added that the cost-effective approaches used to make choices in healthcare should be made explicit and the price differential should always be highlighted. This would allow the avoidance of a utility loss for no gains[106] :

The role of the State

P4 mentioned a difference between the role of the State and the role of stakeholders. At the State level, different mechanisms exist in order to facilitate the social acceptability of constraints on individual choices like the generalization of generic drugs instead of princeps. The use of generic drugs is facilitated on a social level by legal "*inducements, substitution, communication campaigns or constraints*" which in turn influences individual behaviours. By contrast, the social acceptability of biosimilars has been lower in France, certainly due to the absence of incentivization from the State compared to the generic drugs which have been assessed as having the same rate of utility loss but are much more accepted by stakeholders.

Sustainability of the healthcare system

P1 and P2 mentioned the idea of "more is not always better" in healthcare. In a context of limited resources, it is impossible to always do the maximum for each individual in the collective; it can also lead to a loss of utility at the collective level to always try to do more in particular situations

[104] « *Dans le quotidien des médecins je trouve que le médecin est souvent confronté à ça parce qu'il a affaire à des ressources limitées qui sont simplement son temps* ») ; "*Cela m'a beaucoup intéressé quand j'ai vu votre message parce que j'ai l'impression que c'était un peu… ces situations-là sont un peu des tabous*" or « *Je partage assez le point de vue qu'en fait on le fait un peu comme monsieur Jourdain sans le savoir et que c'est finalement un concept qui percole beaucoup plus qu'on ne le pense* ».

[105] « *Je pense par exemple à des hôpitaux qui s'équipent, souvent ils choisissent d'acheter un matériel plutôt qu'un autre et il doit bien y avoir des situations où l'on est dans ces situations-là bien qu'on ne le dise pas ».*

[106] "*Pour revenir sur le côté monsieur Jourdain du décideur dans ces questions-là, je pense qu'il y a une situation pour laquelle on jette un voile pudique, mais dans laquelle non seulement on accepte une intervention avec un décrément d'efficacité ou d'utilité, mais dans laquelle on ne négocie même pas des économies, on n'en a aucune notion, et c'est notamment toutes les interventions […] pour lesquelles on accepte une étude de non-infériorité* » ; "*Mais je crois qu'elle* [cette recherche] *dénote une maturité qui est très loin, même si ce n'est pas un scoop, d'être celle de la réalité des choses et des décideurs et qu'il y a aussi des situations ou finalement on prend ces décisions là sans en avoir conscience et sans… au moins récupérer un peu d'économies* ».

(illustrated by the case of therapeutic de-escalation which considers an intervention as sufficiently effective at some point[107]. A "fair" healthcare system can rely on a careful alignment between ends and means. Therefore, it can be ensured by a reorganization of the available resources or by the reallocation of the collective gains with a special emphasis on the criteria underlining this reallocation.

Covid-19

Five participants expressed views when addressing the AstraZeneca vaccine as a possible case-study for a non-pharmaceutical d-CEI. P2, P4 and P7 considered it as a suitable example at both a micro level (the individual behaviour) and macro level (the UK governmental strategy which relied on spacing injections for increasing individual access). They highlighted for both levels that the choice to protect more individuals with interventions could be considered as providing lower health gains in a context of limited resources. P6 further pointed out that it is a recent health intervention which will need more background clinical information to understand the link between the characteristics of the case and whether it can be considered as a decrementally cost-effective approach. P1 mentioned that the recent AZ vaccine's criticisms, and its low social acceptability, may represent a risk of blurring the discussion on d-CEIs.

In conclusion, policymakers and researchers who participated in the workshop underlined that, in their view, d-CEIs already have a greater play in healthcare than it might first appear. Participants emphasized the importance of framing decrementally cost-effective practices with transparent criteria. The examples of generics and biosimilars were discussed as an illustration of two candidate d-CEIs, offering comparable prospects of cost-savings, the former being actively implemented by the State (using legislative tools and incentivizing patients and prescribers) compared to the latter.

Decision-makers highlighted the utility of the discrete choice experiment, which can contribute to a better understanding of d-CEIs and to open public discussions on the conditions under which a d-CEI could be considered and adopted.

[107] "*J'ai trouvé que c'était une super idée parce que votre démarche va complètement dans le sens de la désescalade thérapeutique*".

Although considering that d-CEIs are already used in healthcare, discussions suggested that this may be done so implicitly; as a result, the lack of guidance and reference practices might lead to a "taboo" or arbitrariness. The discussion with decision-makers allowed for the identification of the following domains where guidance would be needed in order to meet two requirements, namely patient safety and the cost-effectiveness of the alternatives uses to which cost-savings are reallocated: eligible populations, information on the cost-savings, information on the aim of reallocation, common thresholds. In that sense, the definition of tools that decision-makers can use could lead to improvements in the use of d-CEIs in a democratic way for transparent reallocation purposes.

General conclusion

While evidence is growing on the cost-effectiveness of decrementally cost-effective interventions (d-CEIs), as shown in task 1 of WP11, with an increasing consensus on their potential value at enhancing both efficiency and equity of healthcare systems, there is still today a lack of guidance in HTA agencies, including among the "forerunners", on how to consider and legitimately adopt d-CEIs. The consideration, and possible adoption of d-CEIs is still not addressed in the EUnetHTA core model, nor is it precisely defined in NICE[108] guidelines. Moreover, a 2020 review on CHTE methods[109] indicates the need for further guidance on how society may consider that the cost savings compensate for the lower effectiveness in d-CEIs. In fact, assessments of such interventions which lie in the S-W quadrant, implying small health losses for large savings, are most often considered as 'unethical', with the S-W quadrant being seen as a no-go area, or the 'Wild West' by most policy-makers. The potential of d-CEIs remains thus underexploited in all EU countries and internationally.

This political economy report has inquired into the reasons for such underuse, offering different disciplinary contributions, using qualitative and quantitative methods. It has explicitly **addressed the following question: under which conditions will a decision-maker consider, and possibly adopt a d-CEI**. Based on these findings, recommendations are offered in order to encourage d-CEIs' appropriate use and toolboxes are designed to contribute to the implementation of these recommendations (see D11.3).

1 - Mainstreaming: when deciding about the implementation of a new intervention, decision-makers shall be encouraged to systematically consider d-CEIs as ethically licit and politically acceptable alternatives to usual care[110]. The objective is to make d-CEIs "mainstream", thereby

[108] NICE's guidelines manual states that such interventions should be recommended if they free up sufficient resources that can be re-invested in public sector care or services to increase the welfare of the population receiving care.

[109] CHTE methods review, Decision making, Task and finish group report, September 2020, item 1.4.

[110] Mainstreaming is inspired by WHO approach to gender mainstreaming which aims at increasing awareness of existing gender biases in various situations or productions. A parallel can be made with d-CEIs which are not systematically considered when defining the set of alternatives and comparators for a given therapeutic objective.

ensuring that they are systematically considered when defining the range of alternative treatments. Decision-makers will be encouraged to pay attention to how different healthcare systems might condition their willingness to consider the implementation of d-CEIs. By doing so, they may better prevent decisional biases and improve their ability to reach inclusive and evidence-based decisions.

2– Inclusiveness and transparency: For successful implementation of d-CEIs, decision-makers shall be encouraged to actively involve all stakeholders early on in the decision-making process. Discussing the objectives and potential benefits of adopting a d-CEI helps focusing on priority needs and on inequities to redress. Transparency in the deliberation that governs decisions is an important component in securing stakeholders' understanding, participation in documenting the stakes (e.g. disease experience), and possible adherence in case of adoption.

3 – Exhaustivity: All forms of d-CEIs should be considered, such as complementary non-pharmaceutical interventions or stepped care approaches, which imply that disease level should be monitored and treatment adjusted accordingly, stepping up when more intensive treatments are deemed necessary, stepping down where less intensive treatments become appropriate, stepping out when an alternative – possibly non-pharmaceutical intervention, or when watchful waiting, is appropriate.

4 – Social justice and ethics: Mainstreaming d-CEIs in the HTA process should provide an incentive to explicitly discuss the underlying value-judgements, ethical and social justice principles considered in the anticipated savings reallocation.

Three complementary tools have been designed to serve the purpose of encouraging appropriate and acceptable use of d-CEIs. They are defined along the three stages of the decision pathway, from discussion to consideration, and from there to adoption. The first tool is the actual **discrete choice experiment**, which has been perceived by decision-makers as particularly useful in opening the public debate on d-CIEs. The second tool, in the form of a **check-list**, is aimed at those who define the set of alternative treatments for a given condition, in order to ensure that d-CEIs are systematically considered. It contributes to the implementation of the four afore-mentioned recommendations. The third tool is a **decision-tree**, covering the final stage of the decision to adopt, with attributes' rankings defined on the basis of the findings from the discrete choice experiment. The **final decision to adopt**, based on the evidence provided by economic and ethical

considerations, remains entirely with the policy-maker, who seeks a delicate balance between stakeholders' interests.

Multi-disciplinary research in d-CEIs is just beginning. WP11 has attempted to fill this gap by using behavioral economics methods to investigate decision-makers preferences and by initiating a dialogue based on the results of the discrete choice experiment. Workshops have shown the potential of the experiment to illustrate the interplay of individual and collective preferences and the potential value of d-CEIs but also their risk of being simply associated to cost-containment or rationing. More collaborative research action is needed, jointly with HTA agencies, in order to further investigate the willingness of decision-makers in the European Union to consider the implementation of d-CEIs according to the specifics of their national healthcare systems and of the institutional differences in their legal systems. To do so, the current research could be enhanced by improving the current European representativeness of the discrete-choice experiment results, by reaching out to lay persons, in order to document population preferences, to be compared with those of decision-makers, and by further expanding research to mixed approaches, such as stepped care or combined use of pharmaceutical and non-pharmaceutical interventions.

Appendices

Appendix A. Systematic literature review on d-CEIs

The comprehensive overview and contextual data collection were first informed by a systematic literature review carried out by the URC-eco /AP-HP. This systematic literature review identified and categorize interventions offering prospects for cost-effectiveness gains outside incremental innovations captured in the N-E quadrant. After filtering 3,689 studies through a systematic process, 86 decrementally Cost-Effective (d-CE) interventions were selected, based on the following criteria:

1. The intervention is applied to human subjects.
2. Studies include full economic evaluations, thus comparing at least two Health Technologies (HTs): model or trial-based (or mixed), cost-minimization, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) or cost-consequence analysis.
3. The interventions were evaluated in a country identified as an upper-middle-income or high-income economy by the World Bank's 2018 country classification by income level.
4. The interventions were traditional HTs according to the WHO definition - Health technology: "the application of organized knowledge and skills in the form of medicines, medical devices, vaccines, procedures and systems developed to solve a health problem and improve quality of life" (http://www.who.int/health-technology-assessment/about/healthtechnology/en/). We included Non-Pharmaceutical Interventions (NPIs) such as physical activity, diet, psycho-social support or patient education.
5. Studies demonstrated d-CE interventions.
6. Studies are in English.

From the 86 d-CE interventions, 16 were selected to inform the choice of attributes and levels for the DCE. Three criteria were used for the selection:

1. High d-CE ratios;
2. Preferably RCT-based evaluations;
3. Full economic evaluations with reported ICER/ICUR.

As a second step, a scoping literature review was carried out as a complementary contextual data collection for the design of the Discrete Choice Experiment; it focused on studies exploring policy-

makers' stated preferences. The research was carried out on Econlit, using the following algorithm: (Discrete choice experiment OR best-worst scaling OR stated OR revealed) AND (Decision*maker* OR policy mak* OR policy*mak*) AND (preference method). The search was conducted within the following field: “Select a field (optional)” since it covers: author, subject, keywords, title (including source title) and abstract, but NOT the full text. The search was carried out in the EBSCO database, which is “the leading provider of research databases, e-journals, magazine subscription, e-books and discovery service to libraries of all kinds”.[111] Most articles did not have keywords. The search produced 1422 results. The search field was limited to 'abstract' to reduce the number of results to 80 items. We retrieved 15 (out of the 80) by abstracts selection, searching for stated preferences studies involving policy-makers. The 15 articles were used to give an overview of how stated preference methods have been previously used to elicit preferences from policy-makers. We also collected and analyzed the attributes and levels that had been most commonly used for this purpose.

[111] EBSCO research database: https://www.ebsco.com/products/research-databases

Appendix B. Comparison of econometric specifications for the "savings" attribute

	Model 1 (savings categorical)		**Model 2** (savings linear)		**Model 3** (savings non linear)	
	Mean (SE)	SD (SE)	Mean (SE)	SD (SE)	Mean (SE)	SD (SE)
Health loss: very small	*Ref*		*Ref*		*Ref*	
Health loss: small	-1.413***	0.347	-1.438***	-0.451	-1.419***	-0.452
	(0.207)	(0.458)	(0.202)	(0.334)	(0.207)	(0.338)
Health loss: significant	-5.586***	2.814***	-5.849***	2.983***	-5.819***	3.002***
	(0.622)	(0.491)	(0.644)	(0.499)	(0.652)	(0.515)
Reversibility: possible, at any time	*Ref*		*Ref*		*Ref*	
Reversibility: possible, with delay	-1.237***	-0.206	-1.278***	0.270	-1.295***	0.297
	(0.199)	(0.508)	(0.200)	(0.440)	(0.204)	(0.443)
Reversibility: hardly possible, due to long delays	-2.906***	0.680**	-3.020***	0.867***	-3.014***	0.841***
	(0.312)	(0.329)	(0.314)	(0.294)	(0.317)	(0.297)
Savings: 5% of fixed budget	*Ref*					
Savings: 10% of fixed budget	1.238***	0.875	-			
	(0.456)	(0.646)				
Savings: 15% of fixed budget	2.017***	1.300***	-			
	(0.288)	(0.302)				
Savings (linear, per 5% of budget)			1.006***	0.710***	2.228	0.711***
			(0.138)	(0.144)	(1.688)	(0.150)
Savings^2	-		-		-0.308	0.028
					(0.423)	(0.083)
N (individuals)	156		156		156	
Choice observations	1,222		1,222		1,222	
Log-likelihood	-475.29		-471.74		-471.43	

Appendix C. Proportionate Universalism

It is generally accepted that the more disadvantaged one is, the worse health one experiences. Numerous studies and reports show that efforts to remedy health inequities has not ameliorated the social gradient in health. With health care costs increasing an apparent link is emerging with more costs associated with higher needs. So, how to remedy population health disparities? Michael Marmot (2010) in his report "*Fair Society, Health Lives"* suggested Proportional Universalism (PU) can reduce health disparities. Using this approach entails universal action adapted to need and disadvantage. More specifically ***"Actions should be universal, but with an intensity and a scale that is proportional to the level of disadvantage".*** Marmot (2010) argues that policies focusing solely on the most disadvantaged are bound to fail; rather greater intensity of action is needed for those experiencing the greatest social and economic disparities. Since 2010, PU has gained increased traction in policy and research circles. But what is PU in practice? How can this idea be developed to reduce health disparities between income socio-economic groups?

Conceptual issues

Proportional universalism risks being reduced to health policies and interventions. However, doing so risks ignoring the impact of social determinants of health on the life-course. As Marmot (2018) explained the perspective is not "just about health coverage…. but the social determinants of health across the whole of society". Therefore, reducing PU measures to individual agency rather than collective drivers, or as Marmot calls them "the causes of the causes", risks reproducing the same inequities without truly addressing the wider determinants contributing to poorer health outcomes.

Despite this, a lack of clarity regarding PU's practical applicability remains. Efforts are being made to conceptualize the definition. Benach & Malmusi (2013), for example, divide PU policy applications to two groupings:

1. Policies produce universal exposure or entitlement. There is no special device for disadvantaged groups, but benefits increase through the gradient e.g. population-based cancer screening programs.
2. Universal policies incorporating criteria providing greater resource allocation to populations with higher needs e.g. Adult Social Care Packages.

Francis-Oliviero et al's (2020) review on PU expanded the notion to include the synonyms "progressive universalism" and "targeted universalism" discovering practical interventions used one of these three terms. Within this, two major concepts behind PU were identified; universalism and targeting[112]. According to their review, targeting contains three elements: negative selectivism, positive selectivism, and particularism. Negative selectivism includes means-testing, positive selectivism targets need regardless of social position, while particularism "proposes different standards for different categories reflecting diverse circumstances". Marmot (2020) writes that particularism is defined as giving particular groups, or individuals, the capacity or resources to make their own decisions. It can mean differences in the nature and supply of programs which are tailored to different social groups specific needs, whether on the basis of values, ethnicity or other criteria (Monroe). Finally, for Francis-Oliviero et al (2020), a PU approach proposes to focus on upstream health determinants, such as education, employment or neighbourhood renewal with evaluations of need based on income, social category or territory (e.g. Coventry, Wales; see below). Downstream approaches, on the other hand, target access to care or health risk (e.g. Ireland, Scotland; see below).

Proportionate Universalism in Practice

1. Scotland's National Resource Allocation Committee (NRAC) Formula, implemented in 2009, is argued to follow the ***Proportionate Universalism*** concept (MacDonald et al, 2014). NRAC is believed to be an equitable mechanism dividing resources in Scotland's decentralized, universal, free health system, across 14 Health Boards (SPICe, 2011). NRAC is a weighted capitation formula; funding is based on an area's resident numbers accounting for morbidity and deprivation adjusting for relative health needs (SPICe, 2011). Sex/age profile and excess service provision costs of each area are accounted for (isdscotland, 2016a). Calculations are carried out separately for different care programs such as Care of the Elderly and GP Prescribing (isdscotland, 2016b). 70% of NHS Scotland funding is determined by the Scottish Government using NRAC (MacDonald et al, 2014). The WHO

[112] Controversies around targeting distinguish means testing as separate given the focus on income to the exclusion of other characteristics (location, gender, etc.). Consequently, progressive universalism is a universal policy framework where extra benefits and services disproportionately help the less privileged without stigmatization. See Francis-Oliviero, Cambon et al (2020) for full discussion.

praised NRAC for taking better consideration of subgroups' higher relative needs, for accurately reflecting higher health needs in deprived areas, and for compensating for health service under-use in some areas (WHO, 2012).

2. *Republic of Ireland's* health system is typified as public, universal and decentralized with financial costs for treatment and diagnosis. To negate health inequities a complicated system of ***positive and negative selectivism***, largely based on income, has emerged. Free, and tiered, access is determined by sorting patients into two groups; Medical Card or a GP Visit Card holder. Cards determine which aspect of the health system is free, or not, for the holder and level of costs. Eligibility for both cards is means-tested. However, income testing can be waived for specific subgroups or under special circumstances. Term limits are generally applied to card holders with access based on reassessment. A further scheme based on positive selectivism exists where universal, non-means-tested, free access is provided for some drugs, medicines and approved appliances depending on long term chronic illnesses and disabilities.[113]

3. New funding models for Welsh Third level students living costs, implemented in 2018, is considered as a **Progressive Universalist** policy measure (HEPI, 2018). Under this model all students, irrespective of household income are entitled to annual maintenance support, depending on living arrangements, of over £12,000[114] during studies. Maintenance support comprises two parts: A universal, non-repayable, maintenance grant and a maintenance loan. Proportions of grant and loan depend on the income bracket; low income students receiving higher proportions of the non-repayable maintenance grant. Further non-repayable financial support is available based on parental, disability or income support status[115]. Under this system poor students are expected to see education debts rise by 20% while the richest students' debts will increase by 85% (HEPI, 2018).

[113] Information in this section is collated from a range of pages from www.citizensinformation.ie & www2.hse.ie

[114] Maintenance support does not include tuition fees. https://www.savethestudent.org/student-finance/a-guide-to-student-finance-for-welsh-students.html

[115] See https://www.studentfinancewales.co.uk/undergraduate-students/new-students/what-financial-support-is-available/help-with-living-costs.aspx for full selection criteria.

Here, the financial burden is expected to be more equitable after the study period rather than during university studies.

4. Coventry City Council, a 'Marmot City', began applying Proportional Universalism city wide from 2013 when public health duties were legally delegated to local authorities. No template or framework existed for this approach (Munro, 2020). Coventry firmly embed Marmot principles within an asset-based population health approach in health and wellbeing strategy documents (City of Coventry, 2019b). Emphasis is on partnership working, prevention, consistent, honest and sustainable services focusing on upstream health determinants to reduce the social gradient (City of Coventry, 2019a). One manner of achieving this has been to incentivize commissioned public health services to inbuild selectivism and favour delivery to deprived areas while retaining universality. Marmot (2020) describes Coventry's approach to PU as a combination of "positive selectivism and particularism". Fire Service "Safe and Well" checks target households unlikely to seek help, while a charity initiative to build group and community capacities using existing community assets to address local needs are examples of both approaches (Munro, 2020). Coventry's city-wide PU approach has, so far, demonstrated innovative and new ways of working via charities and businesses to conquer upstream health determinants. Funding is weighted towards populations with higher need in numerous domains including employment, children, families and young people's wellbeing, workplace inequality and gender/ethnic equality (See Munro, 2020 for full overview).

Operational Challenges

None of the examples described are without fault nor operational difficulties. The Scottish model doesn't seemed to have reduced the social gradient within, or between, regions while parity of financial esteem concerns between health services have arisen (Palin, 2019). Moreover, despite the need-based model, all-cause mortality (15-44) has increased since 2013 with mortality rates in most deprived areas 4 times higher than those of least deprived areas. One reason for this could be that Health boards decide financial allocation based on health plans, local priorities and population needs. It seems more specific targeting is needed to reduce health gaps. Targeted screening programs, such as actions by NHS Greater Glasgow and Clyde Public Health Screening Unit, may be one way to address health inequities. Welsh efforts to implement progressive universalism in tertiary education has been critiqued for focusing more on debt levels following education completion and not enough on addressing financial hardship over the study period (HEPI, 2018). This would seem to be a legitimate concern given that financial stress contributes to poorer health

outcomes and is likely to be exacerbated by the transition to adulthood and independent living. Furthermore Coventry's, like other cities[116], attempts to implement the Marmot model, are threatened by ongoing Westminster budget cuts to local authority grants and other funding (Marmot, 2020). From 2010 to 2019, Coventry absorbed a 49% cut to its government grant and a 17% cut to Public Health Grants since 2015 (Munro, 2020). While every effort is being made to protect universal services in deprived areas, budget cuts affect effort via lower human resources and impact long-term sustainability. Finally, Ireland's model does not use ideas from proportional universalism. However, attempts to reduce health inequities prioritizing negative selectivism over positive selectivism warrant further investigation; mortality differences between men, based on disability, of up to 14 years exist. Furthermore, downstream efforts to address health inequalities, in Ireland, have not appeared to solve mortality differences between regions, age groups, or occupation and education level, although limited, in-depth, research appears to be available on this topic (Rigby et al, 2017; CSO, 2017).

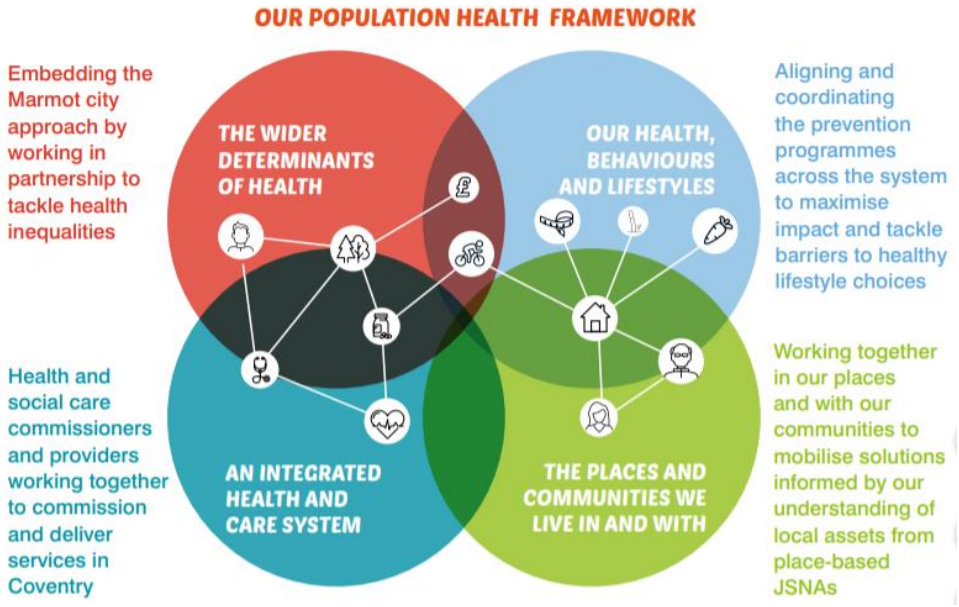
Conclusion:

This paper provided brief conceptualizations and practical applications of Proportional Universalism demonstrating heterogeneity of applications between regions. Each example used variations of PU to tackle health inequities via downstream or upstream determinants. In all scenarios, increased effort almost always concentrated in low-income, deprived groups. However, national/regional disconnects between funding and effort arose in some scenarios with discrepancies between financing and effort.

Further consideration of definitions of need and effort are warranted, especially for measurement purposes, given heterogeneity between and within groups. Additionally, further discussions are required around resource allocation, decision making and the effect that selectivism may have in regions experiencing resource scarcity. Traditionally, targeted interventions have been criticised for focusing solely on lower income as issues concerning stigma and discrimination arise. Efforts to

[116] https://www.equallyours.org.uk/tackling-health-inequalities-marmot-cities/ - Stoke, Newcastle, Gateshead, Bristol, Somerset, Coventry. See Marmot, 2020 & IHE website for further information on programme implementation.

implement PU models need to carefully weigh how to proceed while avoiding the traps identified in this paper.



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