Decision-making for healthcare resource allocation: Joint versus separate decisions on interacting interventions

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Abstract

Standard guidance for allocating healthcare resources based on cost-effectiveness recommends using different decision rules for independent and mutually-exclusive alternatives. However, the definition of "mutually-exclusive" varies. Within this paper, I review the definitions used in the literature and show that interactions are the defining feature of mutually-exclusive alternatives: in other words, treatments cannot be considered independent if the costs and/or benefits of one treatment are affected by whether or not the other is also given. In practice, many interventions given to the same population will have non-additive effects, including prevention, screening and treatment of the same disease, interventions targeting the same goal or clinical event, or life-saving interventions given to overlapping populations. I demonstrate that making separate decisions on interventions that actually have non-additive effects can prevent us from maximising health benefits from the budget. By contrast, treating different combinations of independent options as though they were mutually-exclusive makes the analysis more complicated, but still gives the correct conclusion.

I also discuss the implications for decision-making. Health technology assessment organisations, such as NICE, currently make numerous independent decisions on treatments that are likely to have non-additive effects. For example, NICE conduct numerous separate single technology appraisals on treatments used to treat the same condition and independently consider screening and prevention of diseases such as cervical cancer. By ignoring interactions between these treatments, such decisions may not be optimal. Conversely, the World Health Organisation takes account of such interactions within generalised cost-effectiveness analysis when allocating resources across an entire healthcare system, but often relies upon weak evidence about interactions. Within the UK context, more efficient use of healthcare resources could be achieved through greater use of multiple technology appraisals and taking account of interactions when selecting, prioritising and appraising healthcare technologies.

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1 Introduction

It is well-established that the health gains achieved from a fixed healthcare budget are maximised using the following decision rules for allocating resources between *independent* and *mutually-exclusive* alternatives (1-8).[1]

Given a set of *independent* options (a "shopping spree" problem (3, 4, 8)), we can directly compare incremental cost-effectiveness ratios (ICERs) in a league table and adopt treatments successively from the one with the lowest ICER upwards until the budget is exhausted (2-6, 8, 13). If the last treatment is divisible and has constant returns to scale,[2] this approach ensures that we gain the maximum possible health from the available budget (2, 3, 5, 6, 13). If our league table includes all possible alternatives, we can identify a ceiling ratio that represents the shadow price of a QALY, which will be equal to the ICER of the last treatment adopted (which would also be the first to be replaced by any new treatment). This process can be represented graphically on the cost-effectiveness plane (Fig 1), which shows that this approach maximises the health gained from the healthcare budget (by reaching a point as far to the right as possible) while remaining below the dotted budget line. Once we have an estimate of the shadow price of a QALY, we can consider each new treatment individually, adopting it if its ICER is below the ceiling ratio.

Conversely, if we have a set of *mutually-exclusive* alternatives (a "competing-choice" problem (3, 4, 8)), we need to calculate the ICER for each option compared with its next best non-dominated alternative (1-8). This requires us to identify and exclude from consideration treatments that are strongly or extendedly dominated by others, to identify the efficiency or cost-effectiveness frontier (4, 5) or expansion path (15) (Fig 2).

We can then include the ICER for each of the non-dominated treatment options in our league table (1-4, 6, 7), graphically illustrated in Fig 3. However, since options E1-6 are mutually-exclusive, the table presents the incremental cost-effectiveness of each option compared with the next best non-dominated alternative: for example, besides the least expensive (E1), our league table would include ICERs for substituting E3 in place of E1, substituting E4 in place of E3 and substituting E6 in place of E4.

[1] Integer and linear programming methods, which avoid assuming divisibility and constant returns to scale, have also been proposed (9-12); these make similar distinctions between independent and mutually-exclusive treatments (9), but are not discussed in detail in this paper.

[2] Although these assumptions are not realistic, this is unlikely to matter for two reasons. Firstly, within a complete league table of all healthcare interventions, the cost of each individual intervention will be a very small fraction of the total budget: particularly if the cost-effectiveness of individual treatments is stratified, with the ICER for treatment in different patient groups appearing separately in the league table. Secondly, health care systems typically have a soft budget, such that any money left over from one year can be spent in the next (14).

Fig 1: Graphical illustration of the league table approach. The 10 independent options (A-J) are adopted in ascending order of ICER until the budget (the horizontal dotted line) is exhausted. Providing that the options are independent and the last treatment (G) is divisible and has constant returns to scale, this combination of treatments gains more health from the finite budget than any other combination of treatments.

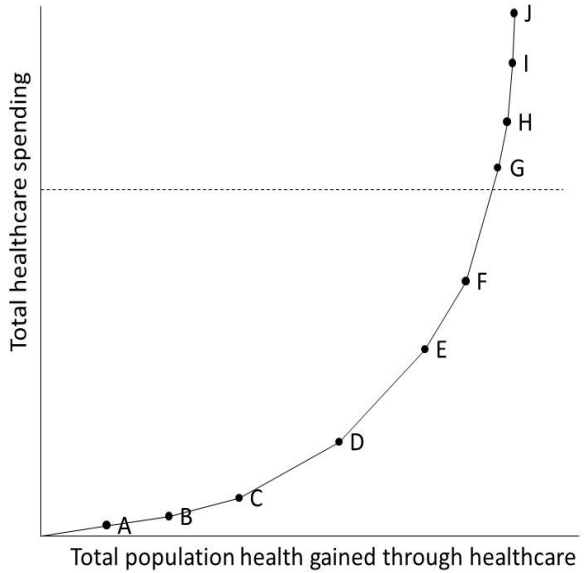


Fig 2: Identification of the cost-effectiveness frontier and dominated options amongst mutually-exclusive alternatives. Within this figure, E2 is extensively dominated by a combination of E1 and E3 (as it lies to the north-west of the line joining E1 and E3), while E5 is strongly dominated by E4 (as it lies to the north-west). The solid line shows the cost-effectiveness frontier.

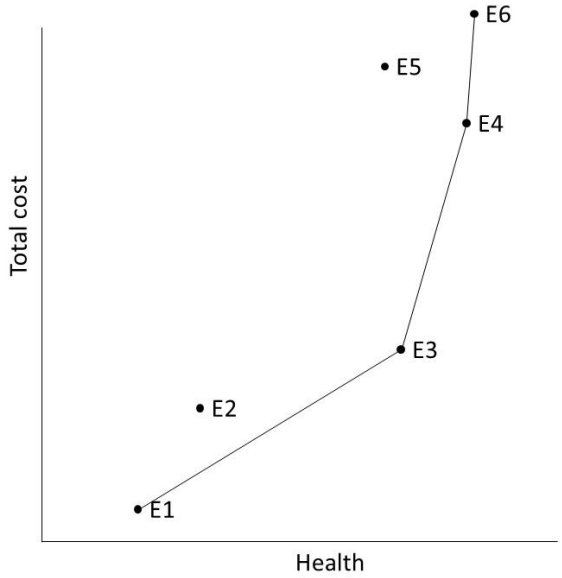
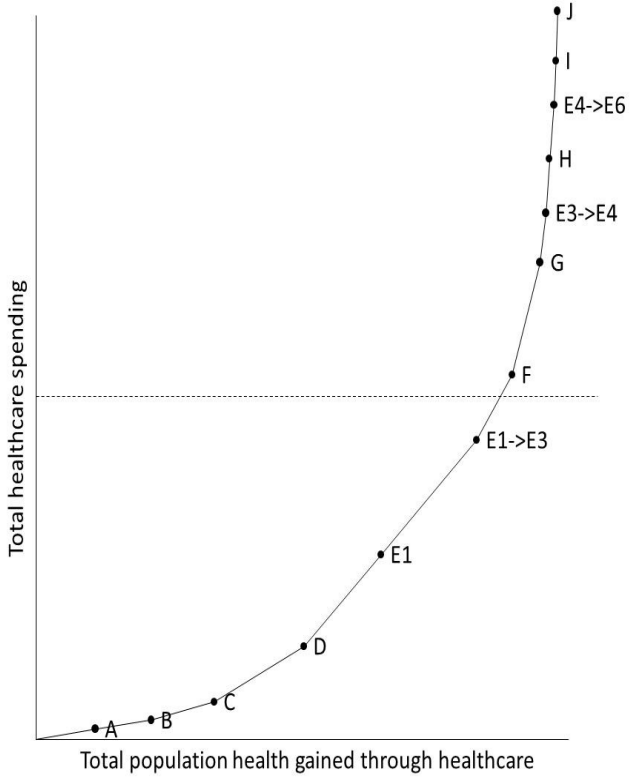


Fig 3: Graphical illustration of a league table with mutually-exclusive options. The ICERs of the three non-dominated mutually-exclusive treatments alternatives to treatment E1 (E3, E4 and E6) are added into the league table; as result, only treatments A-E3 can be fully funded within the same budget (see dotted line).



Alternatively, if a ceiling ratio has already been established, we can simply adopt the most effective treatment that lies on the cost-effectiveness frontier *and* has an ICER below our ceiling ratio (2, 3, 7). This method is simplified further using the net benefit approach, which enables us to simply calculate the net benefits of our six options at the appropriate ceiling ratio and adopt the treatment with highest net benefit (16).[3]

2 Definition of mutually-exclusive and independent alternatives

Although most researchers and teachers of health economics have a reasonable working appreciation of what treatments can be considered "independent" and which are "mutually-exclusive", there is a substantial variation in the definitions used in the literature[4] (Table A1, Appendix). Eleven textbooks or reviews defined "mutually-exclusive" literally, stating that two treatments are mutually-exclusive if patients cannot receive both. However, there are relatively few treatments that are impossible to implement together besides different levels of the same treatment or different approaches to irreversible surgery. Seven other definitions recommend that all treatments given to the same patient population are considered mutually-exclusive. However, 10 of the published definitions make specific reference to non-additive effects (i.e. interactions) as the defining feature that determines whether or not treatments are considered to be mutually-exclusive or independent.

This suggests that whenever treatments interact, we should treat the combinations of inter-related treatments (e.g. no treatment, A, B and A+B) as mutually-exclusive options, comparing the treatment combinations incrementally and selecting the single strategy that maximises net benefit for that population. Conversely, this implies that if there is no interaction between treatments, we should treat A and B as independent treatment options and compare their ICERs against the ceiling ratio separately, adopting those treatments with ICERs below our ceiling ratio (38, 40, 43, 44). However, only the two World Health Organisation (WHO) definitions (15, 19) mentioned the word "interaction" and these use slightly different terminology. Here, distinctions are made between mutually-exclusive treatments (which cannot be implemented together), technologies that can be given together but interact, and independent technologies that do not interact. They recommend that

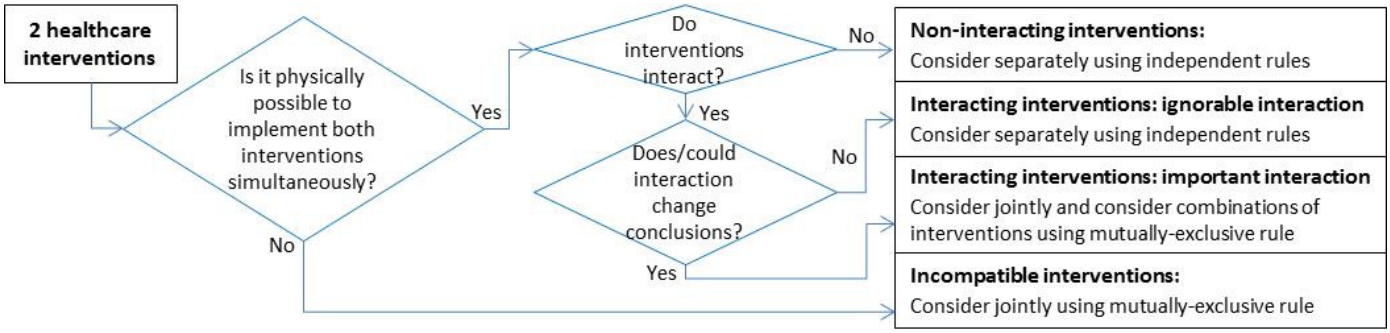
[3] In practice, risk-averse decision-makers may consider the uncertainty around ICERs (17), although I take the view in this paper that inference is irrelevant to treatment adoption decisions (18).

[4] Definitions were identified by searching Google scholar (first 100 hits only) and Medline through PubMed on 5th November 2013 for terms including '"mutually-exclusive" cost-effective', 'independent option cost-effective' and 'independent alternative cost-effective'. Key health economic textbooks and the reference lists from identified papers and books were also reviewed.

combinations of interacting technologies are considered as a "cluster" of inter-dependent interventions and evaluated incrementally like mutually-exclusive alternatives.

I therefore propose using the terms *incompatible*, *interacting* and *non-interacting* (Fig 4). I would be grateful for feedback on this terminology, any definitions I have missed and whether you would have associated the definition of "mutually-exclusive" with interactions.

Fig 4: Flow diagram illustrating proposed terminology and decision rules



3 Situations when interactions are likely

Interactions between treatments may result from pharmacological, behavioural or biological mechanisms (20-22). For example, one drug may reduce or accelerate metabolism of the other, giving a second intervention may affect compliance with the first treatment or biological mechanisms (e.g. homeostasis) may mean that adding drug A in patients already receiving drug B (which targets the same biological marker) has less impact than when A is given alone. However, the interactions brought about by these mechanisms may be relatively small unless drugs are in the same pharmacological class or combination therapy is harmful.

Interactions are also inevitable when treatments have multiplicative effects (20, 22-27): i.e. have a constant proportional effect, which means that there is an interaction on a natural scale, but not on a logarithmic scale. In particular, interventions that affect the risk of clinical events (e.g. death or stroke) generally have multiplicative effects on outcome (21, 28), increasing or decreasing risk, odds or hazard by a certain percentage. This means that the absolute effect of treatment is larger for high-risk patients and smaller for patients who are already receiving treatment. For example, two interventions (e.g. antihypertensives and statins) may both reduce the risk of stroke by a certain percentage, which means that the cost-savings and QALY gains from using antihypertensives to prevent stroke will be smaller if patients also received concomitant statins. Similarly, all life-extending treatments are likely to have multiplicative effects on all-cause mortality. Although this type of interaction can be eliminated by analysing results on a logarithmic scale (20, 22-27), this is not feasible for

economic evaluation, where we need to draw conclusions about cost-effectiveness based on absolute costs and absolute QALYs.[5]

Interventions that extend life expectancy will also increase the QALY gains from other interventions that improve quality of life (and vice versa), since QALYs equal length of life multiplied by quality of life. Treatments also often have multiplicative effects on cost (30). Adding additional healthcare interventions may also give diminishing (or increasing) marginal returns for utilities (31, 32), which are built into utility measures (e.g. EQ-5D and HUI): e.g. as people may experience a larger improvement in quality of life from the first intervention than they will from any subsequent one.

Patient pathways can also introduce interactions. For example, the costs and benefits of screening will always depend on the prevalence of the condition and on what interventions are used to diagnose and treat the cases identified (33). At the extreme, screening is of negligible value if there is no effective treatment (33), or if preventative treatments have eradicated the disease in this population. Similarly, the costs and benefits of preventative interventions will depend on the costs and effectiveness of subsequent diagnosis and treatment: e.g. prevention may have little value if there is a cheap, highly effective cure. The costs, benefits and range of options for second-line therapy may also be affected by what treatment was given first-line: particularly if drug resistance develops.

Interactions between treatments can also arise from interactions between diseases: for example if having heart failure changes the risk, case-fatality, cost or quality of life associated with stroke (34), interventions reducing the risk of heart failure will also indirectly affect the cost-effectiveness of treatments to prevent and/or treat stroke, even if they do not directly influence the incidence of stroke in patients without comorbid heart failure. Increasing the cost of treatment for any common condition by introducing new interventions will also increase the cost accrued in the years of life gained from any life-saving treatment if future costs (35) are included in analysis.

Whereas the above types of interaction arise between treatments given to the same patients, interactions are also possible even between treatments given to different patient groups within the same healthcare system. For example, freeing up hospital beds through conducting a surgical procedure as a day-case may increase costs and, potentially, health

[5] Resource allocation decisions must be based on costs and QALYs measured on a natural scale (29). In particular, setting the ceiling ratio or allocating resources using a league table approach (1, 4) necessarily requires *adding* the total budget implications of each treatment to the total already spent. Similarly, if we wish to maximise health gains from the fixed budget, we need to compare the ratio of incremental costs and income and QALYs on natural scales against a ceiling ratio representing the shadow price of a QALY.

benefits of other forms of surgery if patients undergoing other procedures stay in hospital longer once more beds are available, or if reducing bed-occupancy has a non-linear effect on the cost/bed-day. Equipment purchased for one intervention can also be used for other patients, which may affect their costs and health gains. Complex interventions and changes to how services are delivered or organised will also change the costs and benefits of numerous interventions: for example, setting up or reorganising a primary care service to offer measles vaccination may change the feasibility, cost and outcomes of tuberculosis treatment that is then delivered in the same centre. Similarly, nurse-led measures to encourage women to check for breast cancer may increase the chance that the same nurses promote awareness and routine checks for other diseases. Conversely, adding an additional intervention into a health care package (e.g. primary care services) may affect compliance and introduce interactions between the new service and existing ones delivered by the same healthcare professionals.

However, in practice interactions between treatments given to different patients are likely to be smaller and occur less commonly than interactions between treatments for the same patients and it may therefore be reasonable to exclude them. This trend explains the apparent contradiction between the definitions described in Section 2: since economically-important interactions are substantially more likely between treatments given to the same patients than treatments given to different patients, patient group is a useful rule of thumb to identify the situations in which treatments should be considered mutually-exclusive. Since interactions cannot be ruled out whenever two treatments are given to the same patients, there is an argument for treating all treatments or treatment combinations given to the same patient group as mutually-exclusive.

4 Implications of using the "wrong" decision rule

At present, health technology assessment organisations within the UK and other developed countries predominantly make independent decisions about specific technologies: for example assessing one drug at a time compared with its main competitor(s). Since interactions appear to determine which decision-making rule is recommended and are likely to arise commonly for costs and QALYs, I evaluated the implications of using the “wrong” decision rule: i.e. making separate decisions about technologies that interact and making a joint decision between different combinations of independent technologies. This was explored using league tables of 14 hypothetical interventions, of which six pairs of treatments interacted due to the mechanisms described in the previous section; data generating mechanisms can be seen at www.herc.ox.ac.uk/downloads/decisionrules.

Making independent decisions about each treatment

Each of the interventions was first evaluated as though they were independent of all other treatments in the league table (Table 1). Estimating costs and effectiveness separately for interacting treatments highlights the first difficulty with this approach: namely that the incremental costs and benefits are sensitive to the proportion of patients who receive the inter-related treatment, which is not specified in the research question.[6] For simplicity, the costs and benefits of each treatment were estimated under the assumption that 50% of eligible patients received the inter-related treatment and 50% did not. For example, the incremental cost of statins vs. no statins (£1.96 billion) was estimated as the average of statins+antihypertensive (£3.42 billion) and statins alone (£2.42 billion) minus the average of antihypertensive alone (£1.42 billion) and no treatment (£500 million), assuming that 50% of patients received antihypertensives.

Given a £3.5 billion budget and making independent decisions about inter-related treatments, the league table showing the incremental costs and benefits of the 14 interventions (Table 1) would lead us to adopt the 11 treatments with lowest ICERs and partially-adopt antihypertensive treatment,[7] gaining 5.254 million QALYs compared with adopting no treatments.

Treating all treatments as inter-related

This resource allocation was contrasted with an analysis allowing for interactions between the same seven pairs of inter-related treatments by explicitly modelling different combinations with and without these pairs of treatments (Table 2). Although Table 2 was generated using the same underlying data, incremental costs, QALYs and cost-effectiveness differ from those in Table 1 since each combination of treatments is considered separately. For example in cluster A, Table 1 shows the incremental costs and QALYs for statin vs. no statins averaged across patients with/without antihypertensives, whereas Table 2 shows the incremental cost and QALYs for antihypertensive (without statin) vs. no treatment, statin (without antihypertensive) vs. antihypertensive and for statin + antihypertensive vs. statin.[8]

[6] In practice, the proportion of patients receiving the inter-related treatment could be anywhere between 0% and 100%, depending on what proportion of patients in the population of interest are indicated for the inter-related treatment and what proportion of eligible patients receive this treatment in practice.

[7] When using the league tables, I assume that the last treatment adopted (in this case antihypertensive) is divisible and has constant returns to scale.

[8] For example, the incremental cost of statin only vs. no treatment (£996 million) equals the cost of antihypertensive only (£2.42 billion) minus the cost of no treatment (£1.42 billion).

Table 1: League table assuming that all treatments are independent. Treatments that would be adopted are shown in green, treatments that would be partially-adopted in black and treatments not adopted in red. Adopting A1 in 6% of patients as well as the treatments in green gains 5,254 QALYs.

Treatment	Total Δ cost '000s	Total Δ QALYs '000s	ICER	Cumulative cost '000s	Cumulative QALYs '000s
Smoking cessation (B1)	-£9,000	21.60	Dominant	-£9,000	22
Ovarian cancer treatment (G1)	£12,500	50.00	£250	£3,500	72
Cervical cancer screening (F1)	£625,000	1,880	£332	£628,500	1,952
Cervical cancer treatment (F2)	£1,575,000	3,136	£502	£2,203,500	5,088
Knee replacement (B2)	£300,000	151.20	£1,984	£2,503,500	5,239
Antidepressant (E1): Patients with comorbid pain and depression	£5,000	2.00	£2,504	£2,508,500	5,241
Twice-daily treatment for anxiety vs. once-daily (C2)	£2,680	1	£3,350	£2,511,180	5,242
Painkiller 1 (D1): Patients with pain only	£18,000	3.28	£5,496	£2,529,180	5,245
Painkiller (E2): Patients with comorbid pain and depression	£18,000	2.65	£6,792	£2,547,180	5,248
Drug B for anxiety vs. Drug A (C1)	£840	0	£10,500	£2,548,020	5,248
Painkiller 2 (D2): Patients with pain only	£48,000	3.28	£14,656	£2,596,020	5,251
Antihypertensive (A1)	£963,305	43.90	£21,944	£3,559,325	5,295
Statin (A2)	£1,959,099	76.97	£25,454	£5,518,425	5,372
Benign prostatic hypertrophy treatment (G2)	£116,000	4.00	£29,000	£5,634,425	5,376

Table 2: League table allowing for interactions between clusters of inter-related treatments. Treatments that would be adopted are shown in green, treatments that would be partially-adopted in black and treatments not adopted in red. Dominated options (B2, C2, D2, E2, F2, G1, G2) are omitted. Adopting G3 in 70% of patients as well as the treatments in green gains 5,313 QALYs.

Treatment	Total Δ cost '000s	Total Δ QALYs '000s	ICER	Cumulative cost '000s	Cumulative QALYs '000s
Smoking cessation only (B1) vs. B0	-£9,000	14.40	Dominant	-£9,000	14
Ovarian cancer treatment only (G1) vs. G0	£12,500	50.00	£250	£3,500	64
Cervical screening and new cervical cancer treatment (F3) vs. F0	£2,200,000	5,016	£439	£2,203,500	5,080
Knee replacement + smoking cessation (B3) vs. B1	£300,000	158.40	£1,894	£2,503,500	5,239
Twice-daily Drug A for anxiety (C2) vs. C0	£1,840	0.72	£3,000	£2,505,340	5,240
Painkiller 1 only (D1) vs. D0: Patients with pain only	£18,000	5.32	£3,383	£2,523,340	5,245
Antidepressant only (E1) vs. E0: Patients with comorbid pain and depression	£5,000	1.10	£4,545	£2,528,340	5,246
Painkiller + antidepressant (E3) vs. E1: Patients with comorbid pain and depression	£18,000	3.55	£5,075	£2,546,340	5,249
Twice-daily Drug B for anxiety (C3) vs. C2	£2,960	0.80	£14,000	£2,549,300	5,250
Antihypertensive only (A1) vs. A0	£916,429	59.52	£15,396	£3,465,729	5,310
Ovarian cancer treatment + benign prostatic hypertrophy treatment (G3) vs. G1	£116,000	4.00	£29,000	£3,581,729	5,314
Statin only (A2) vs. A1	£995,794	33.07	£30,113	£4,577,522	5,347
Statin + antihypertensive (A3) vs. A2	£1,010,182	28.27	£35,730	£5,587,705	5,375
Painkillers 1 & 2 (D3) vs. D1: Patients with pain only	£48,000	1.23	£39,024	£5,635,705	5,376

For illustrative purposes, one of the clusters comprised two treatments that can safely be assumed to be completely independent: one treatment for ovarian cancer and another for benign prostatic hypertrophy (BPH). Since there is no interaction between these treatments,

the cost, effectiveness and cost-effectiveness of ovarian cancer treatment is the same regardless of what intervention is given for BPH (and vice versa, Tables 1 and 2).

Given the same £3.5 billion budget, a league table allowing for interactions between treatments would lead us to adopt the nine treatments with lowest ICERs and partially-adopt G3, gaining a total of 5.313 million QALYs compared with adopting no treatments: 58,086 (1.1%) more than we would gain by ignoring interactions. This QALY gained is realised by adopting treatment combinations with lower ICERs: for example, using Table 2 we fully adopt antihypertensive treatment and partially implement BPH treatment, but do not adopt painkiller 2.

Making independent decisions on interventions that interact can also give misleading conclusions when decisions are made using a ceiling ratio representing the shadow price of a QALY, rather than a league table. For example, given a £20,000/QALY ceiling ratio, if we evaluated cluster D as mutually-exclusive combinations, we would adopt drug 1 (D1, costing £3,383/QALY vs. D0), in preference to drug 2 (D2, strongly dominated by D1) or combination therapy (D3, costing £39,024/QALY vs. D1); by contrast if the two drugs are evaluated independently, both would be adopted, since both cost <£20,000/QALY vs. no treatment.

However, the two approaches give identical conclusions for interventions that have additive effects on costs or QALYs, with no interaction (e.g. cluster E). The approaches give different adoption decisions only when there are *qualitative* interactions for net benefit at the ceiling ratio of interest: i.e. when the incremental net benefit for A changes sign depending on whether B is also given. This means that the conclusions for interventions that are unambiguously above or below our ceiling ratio (e.g. clusters B, C, F and G) are unaffected (since they do not have a quantitative interaction on net benefit), whereas those for clusters A and D are.

More generally, taking interactions between treatments into account and making a joint decision on all interventions under consideration always enables us to maximise the health gains from our budget. By contrast, ignoring interactions and making independent decisions about interventions that interact can lead to suboptimal resource allocation decisions that do not maximise the health gains. Furthermore, interactions are the reason why treating mutually-exclusive options as independent gives misleading conclusions, as the costs and benefits of Treatment A are assumed to be unaffected by whether or not we also give Treatment B, implicitly assuming zero interaction between A and B.

However, in practice quantifying costs and benefits of all possible combinations of all treatments and quantifying the extent to which costs and effects are affected by all possible concomitant treatment would require additional data or assumptions and make economic evaluation infeasibly complex and expensive. As such, there may be an argument for assuming that treatments are independent in certain circumstances.

5 Current decision-making methods

Current practice: developed countries

At present, HTA organisations such as the National Institute for Health and Care Excellence (NICE) currently make separate resource allocation decisions on different interventions used to treat the same conditions. NICE increasingly conduct single technology appraisals (STAs) evaluating one drug at a time, in preference to multiple technology appraisals (MTAs) evaluating a whole treatment class simultaneously, or guidelines evaluating all treatments and care pathways for a particular condition. For example, NICE made separate recommendations on cervical cancer screening (TA69) and cervical cancer treatment (TA183), which did not explicitly discuss interactions between treatments.

Making separate decisions on treatments for the same condition has several implications. Firstly, considering treatments one at a time means that the study question does not explicitly address what, if any, other interventions are given alongside and means that interactions between interventions are likely to be ignored, leading to suboptimal decision-making, as described in the previous section.

Secondly, recommendations and guidance based on separate decisions frequently do not explicitly state whether treatments are recommended alone or in combination with other treatments. For example, NICE commonly recommends treatments "as an option for the treatment of" the condition in question, without explicitly discussing what if any concomitant treatment is assumed or recommended.

Thirdly, even in situations where combination therapy is inappropriate, evaluating drugs one-at-a-time means that treatment A is not always considered as a comparator when B is being evaluated, which may mean that dominance is overlooked and that ICERs are calculated relative to a comparator that does not lie on the cost-effectiveness frontier. For example, NICE evaluated tenofovir and entecavir in separate STAs and recommended both treatments for hepatitis B (36, 37), despite entecavir being substantially more costly, with no evidence of higher efficacy (38).

However, making separate decisions on different treatments will simplify decision-making and enable decisions to be made quickly by different teams. Furthermore, NICE's preference for recommending several options for the same condition may reflect a reluctance to recommend one treatment over another without head-to-head evidence demonstrating statistically significant superiority. Recommending several treatments also enables patients and clinicians to choose the most appropriate treatment, decreases the number of politically-damaging "no" decisions and avoids conflict with the pharmaceutical industry.

Current practice: WHO

By contrast, the WHO framework for generalised cost-effectiveness analysis (GCEA) models clusters of inter-related treatments simultaneously, and explicitly allows for interactions between interventions (14, 15). The WHO intend GCEA to provide estimates of relative costs and effectiveness "that are meant to contribute through multiple channels to a more informed debate on resource allocation priorities" (14, 15) and which are broadly applicable across a wide range of countries. Different combinations of interventions are compared against a "null", which comprises costs and health benefits if the entire cluster of interventions was withdrawn, in order to assess the cost-effectiveness of current interventions and ensure that results can be generalised to other populations. The WHO population model PopMod also directly allows for different types of interactions between diseases (34).

The WHO-CHOICE programme has now evaluated 15 large clusters of interventions for up to 14 different regions (http://www.who.int/choice/results/en). However, the results for any given region will only give a broad indication of the cost-effectiveness for any given country. Furthermore, the evidence on interactions is frequently weak and relies upon assumptions of multiplicative effects (15, 39). Indeed, WHO explicitly aim to simply identify the "order of magnitude differences in cost-effectiveness of different interventions" and categorise interventions into "good buys" and "bad buys" to guide decision-making processes that also consider equity considerations and other constraints.

6 A proposed alternative

The analyses described above suggest that it is always correct to treat the options as mutually-exclusive, but that making separate decisions on inter-dependent treatments and failing to consider interactions will fail to maximise health gains from the budget. One option for ensuring efficient resource allocation would therefore be to consider *all* combinations of all possible interventions as mutually-exclusive alternatives, although this is unlikely to be feasible in practice. Instead, the flow chart in Fig 4 could be followed to allow for those

interactions likely to change the conclusions of the analysis and ignore small, unimportant interactions. Several changes could be made to the current NICE process to allow for these important interactions in decision-making.

The single most important change is to consider the likelihood, type and magnitude of interactions with other interventions at all stages in the appraisal process. In particular, considering interactions at the pre-scoping or horizon-scanning stage will enable identification of interventions that have no major interactions and can be evaluated separately. While all interventions given to overlapping populations are likely to interact to some extent (e.g. through impacts on mortality), such interactions may frequently be small and unlikely to change the conclusions of the analysis: particularly if interventions have only a small impact on total life expectancy or if the overlap in the populations is small. It may therefore be appropriate to make a pragmatic decision about whether or not the added complexity of making a joint decision is justified given the strength of interactions (15). Some decisions may also be inter-dependent in the long-term, but independent in the short-term. For example, the cost-effectiveness of screening for cervical cancer will depend on the availability and coverage of human papillomavirus (HPV) vaccination, which will reduce the incidence, while the cost-effectiveness of vaccination will depend on what screening is made available in the future. However given the substantial delay between vaccination at age 12-13 and screening from age 25, it is reasonable to make separate decisions about vaccination and screening today, providing that these are reviewed regularly to allow for changes in the incidence and treatment patterns.

Considering interactions at the pre-scoping or horizon-scanning stage can also enable technologies to be evaluated as MTAs rather than STAs to facilitate simultaneous decisions on multiple treatments, or to be evaluated as clinical guidelines that consider the condition as a whole. Technologies that are specifically dependent on certain other interventions can also be identified at this stage, which may affect the sequencing of appraisals. For example, the options for cervical cancer treatment could be appraised first and the appraisal on screening strategies could be started after the former appraisal was completed, in order to assess the cost-effectiveness of screening, conditional on having already adopted the most cost-effective strategy for treating the cancers detected. It may also be appropriate to schedule appraisals evaluating first-line treatment before appraisals evaluating second or subsequent-line treatment, which can then be conditional on the first-line recommendations.

Identifying likely interactions at the scoping stage can also ensure that manufacturers and academic groups take these into account in the analysis and address the most appropriate

research questions. In particular, many interactions between treatments can be eliminated by allowing for heterogeneity and making stratified decisions specific to patients in different risk groups or stages. For example, the cost-effectiveness of statins will depend on whether or not aspirin and antihypertensives are also administered, since these will all affect patients' cardiovascular risk. However, if we make stratified decisions for patients at different risk levels, the cost-effectiveness of statins *at any given level of risk* may be independent of other preventative treatments. Stratified decisions can also eliminate other types of interaction: e.g. decisions could be stratified by life expectancy or all-cause mortality. Stratifying decisions by stage of cancer can also ensure that the decision about treatment of cancer is conditionally independent of screening. Screening may increase the chance that cancers are detected at an early stage, thereby affecting the costs and benefits of treatment when averaged over all stages. However, if costs, quality of life and mortality *within* any given stage are independent of screening, we can make stratified decisions about the appropriate treatment for any given stage that are then independent of what screening is offered.

Even after ignoring unimportant interactions, sequencing decisions logically and making stratified decisions, some clusters of treatments will still need to be evaluated jointly. This group is likely to include treatments that have non-additive effects on quality of life (e.g. clusters C and D) and interactions between prevention and screening/treatment when there is little delay before onset of disease (e.g. vaccination and prophylactic treatment for influenza). In some of these cases, decisions could be stratified by whether or not concomitant treatment is received, although it is likely to be more informative to make a joint decision on both treatments simultaneously, since both are amenable to decision-maker control.

Sources of evidence on interactions

Preliminary estimates of the importance of interactions and modelling work to estimate the incremental costs and effects both require evidence on the magnitude and direction of interactions. As illustrated in Section 4, the conclusions of economic evaluations will often be sensitive to the assumptions made about interactions. In principle, making an extremely inaccurate assumption about the magnitude or direction of interactions could give more misleading conclusions than ignoring interactions altogether. However, this is not a good reason to make separate decisions on interacting treatments, since making a joint decision between mutually-exclusive combinations forces us to explicitly consider the direction and magnitude of interactions and prompts collection of evidence on interactions and

consideration of the uncertainty around the interaction rather than simply assuming that the interaction is exactly equal to zero.

The best evidence on interactions will come from adequately-powered factorial randomised controlled trials (RCTs) (21): i.e. multi-arm studies comparing combinations of two or more factors, or treatments. Factorial RCTs provide an unbiased estimate of the interaction between the two factors as well as evaluating each factor individually. However, most factorial trials are not adequately powered to detect the statistical significance of interactions (21, 40), so cannot conclusively demonstrate whether an observed interaction arose by chance. Factorial trials with economic evaluations can directly assess the magnitude of interactions for costs, QALYs and net benefits; these can also be used to evaluate the cost-effectiveness of both treatments simultaneously, taking into account any observed interaction (41). Nonetheless, even factorial trials lacking prospective collection of resource use or quality of life data can inform the interactions used in model-based economic evaluations. If a factorial trial observes a statistically significant interaction in clinical endpoints, it is clearly appropriate to treat these options as interacting and include the interaction term estimated in that trial as a model parameter and model its effect on costs and effects. However, it may be appropriate to include even non-significant interactions within models and make a joint decision about both treatments evaluated in the factorial trial: particularly as interactions may be larger for costs and QALYs than for clinical endpoints.

Network meta-analyses synthesising evidence on an entire network of treatments evaluated in RCTs (42) can also provide information on interactions. In particular, network meta-analysis can be used to estimate the efficacy of A, B and A+B relative to no treatment based on direct and indirect comparisons comparing different pairs of treatments. Such an analysis could include any available factorial trials and can estimate model inputs that explicitly allow for the fact that A and B may not have additive effects.

In principle, subgroup analyses stratifying patients by concomitant treatment could be used to estimate interactions, although these will not give unbiased estimates of the efficacy of any treatment to which patients were not randomly assigned. For example, a trial randomising patients to receive A or placebo that stratified patients into those who received concomitant B and those who did not, will give unbiased estimates of the efficacy of A vs. no A with/without B and could be used to inform decisions about which patients should receive A. However, this study would not provide an unbiased estimate of the cost-effectiveness of B, or inform a joint decision about whether patients should receive A, B or A+B, since selection bias could confound any differences between the groups with and without B.

There may also be evidence suggesting that treatment has a multiplicative effect on outcomes, such as reducing the rate, odds or probability of clinical events by a certain percentage. Ideally, such evidence would come from factorial trials, or (at a minimum) subgroup analyses or epidemiological studies. Even in the absence of such studies it may be reasonable to assume, as is commonly conducted in WHO-CHOICE studies (15, 39), that treatments affecting the chance of subsequent events have approximately multiplicative effects. However, results will differ depending on whether treatment is assumed to have a multiplicative effect on the hazard, a multiplicative effect on the odds, or a multiplicative effect on the probability, demonstrating the importance of identifying the appropriate scale.[9] Nonetheless, assuming multiplicative effects on any measure of the likelihood of clinical events will be more realistic than assuming additive effects on costs and QALYs when treatments affect the incidence of any common event, such as mortality, uptake of screening or stopping smoking.

Interactions that arise from the clinical pathway can also be built into the model structure based on expert opinion or guidelines. For example, the cost-effectiveness of screening will always depend on what (if any) treatment will be given downstream and second-line treatment will depend on the treatment given first-line. Expert opinion and/or pilot studies could be used to evaluate the impact of service reorganisation or changes to delivery on the costs and benefits of the interventions delivered through that service.

7 Conclusions

In conclusion, interactions determine whether it is appropriate to make independent decisions on different treatments. Making a joint decision on several treatments with appropriate assumptions about interactions will always maximise health gains from the budget, whereas making independent decisions on interacting technologies can (but won't always) lead to inefficient resource allocation decisions. HTA organisations, such as NICE, could improve decision-making by taking account of interactions when selecting, prioritising and appraising health care technologies. In particular, evaluating several technologies simultaneously within a guideline or MTA will encourage analysts and decision-makers to explicitly consider interactions between interventions.

[9] For example, if the odds of death are 0.05 without treatment and A halves the odds of death and B reduces the odds of death by 30%, there will be no interaction for odds on a logarithmic scale (interaction =Ln[0.05]-Ln[0.05*0.5]-Ln[0.05*0.3]+Ln[0.05*0.5*0.3]) . However, if we convert these odds into probabilities (where probability = odds/[1+odds]) or rates (where rate =-Ln[1-probability]), there will be an interaction on a log-probability or log-rate scale.

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Appendix Table A1. Published definitions of "mutually-exclusive" and "independent".

Publication	Definition of "mutually-exclusive"	Definition of "independent"	Type*
Briggs 2000 (43)	"Mutually exclusive programmes involve the same group of patients and, therefore, one or the other must be chosen.	"Independent programmes can be implemented either singly or jointly, so in the case of the ICD, the device could be implanted into patients with a high ejection fraction or those with a low ejection fraction, or into both types of patient.	L P
Carlson 1996 (44)	"The treatments that are available to one patient group are mutually-exclusive, which means that a patient can only receive one of the treatment alternatives"	"The treatment used in one patient group is assumed to be independent of the treatments used in other groups. That is the costs and health effects of a treatment in one patient group are not affected by the treatment alternative chosen in any other patient group"	L I P
Drummond 2005 (1)	"The various alternatives within each programme are assumed to be mutually-exclusive, in that if a patient receives one of the treatments in each programme, they will not receive the others" pages 127-130	"The treatment used in one patient group is assumed to be independent of the treatments used in other groups. That is, the costs and health effects of a treatment in one patient group are not affected by the treatment alternative chosen in any other patient group." pages 127-30	L I P
Elbasha 2004 (45)	"Programs in a cluster are said to be locally mutually exclusive if an individual receives a service of one program, and he/she cannot obtain the service of another program from the same cluster [22]. Examples of locally mutually exclusive programs are cancer detection programs defined by the frequency of screening. An individual cannot be screened both annually and biennially. However, it is assumed that two individuals can receive the services of two different programs from the same cluster. For example, one individual is annually screened, whereas the other is screened every 2 years. That is, programs are not globally mutually exclusive."		L
Evans 2005 (19)	"If one is chosen, another cannot be." "Mutually exclusive interventions must replace an existing intervention" *However, the authors do recommend evaluating all combinations of interventions allowing for interactions*	"Can be done at the same time in a population, with or without interactions. "Can be added to existing interventions"	L I-
Gray 2011 (5)	"Clearly, it would be possible to implement both primary *and* secondary prevention; these are independent policies affecting different patient groups, and so the appropriate approach would not be to calculate the incremental cost-effectiveness of primary versus secondary prevention, but rather to calculate the incremental cost-effectiveness of statins in each relative to the next best alternative for that group of patients. The resulting ICERs could then be compared to see which offered the best value for money. Similarly, policies aimed at different age groups are independent, and a direct incremental calculation of the cost-effectiveness in one age group versus another would not be appropriate. However, different doses of statin are a different matter. Giving a 20 mg/day dose cannot be considered independently of giving the same person a 40 mg/day or 80 mg/day dose; these are mutually-exclusive alternatives." pages 15		L P
Heshmat 2001 (46)	"…Two programs, A and B, are mutually-exclusive if implementing program A (B) means that program B (A) cannot also be implemented. Mutually-exclusive programmes can be viewed as programmes for the same population (e.g. two alternative drugs for ulcer patients)."	"Two programs, A and B, are defined as independent if the costs and effectiveness of programme A (B) are not affected by whether program B (A) is implemented or not. The two programmes are viewed as applying to two different populations; an example being the treatment of ulcer patients and the treatment of arthritis patients...."	L I P
Hunink 2001 (4)	"In many health applications of CEA, however, the choices involve two or more interventions that, by definition, cannot be selected at the same time – not just a yes/no choice for each alternative. The choice among four strategies for breast cancer screening, each involving a different screening interval, is such a choice among mutually-exclusive, or *competing choices*. Another is the choice between two different		L I

Publication	Definition of "mutually-exclusive"	Definition of "independent"	Type*
	surgical procedures. This situation contrasts with the choice facing a public health agency of whether to implement an anti-smoking campaign and/or a skin cancer screening programme, since the decision to perform one service does not inherently preclude a decision to perform the other one […] The basic difference between these situations is that in competing choice situations such as that among breast cancer screening methods, the alternatives are not independent. In other words, the choice of the first alternative influences the benefit to be gained (or the cost incurred) by the second. In a noncompeting situation – such as the public health agency with a financial budget or the clinician with a time budget – the benefits of each programme can be added. In the competing choice situation, they cannot." (page 277)		
Johannesson 1996 (2)	"Two programmes, A and B, are mutually-exclusive if implementing programme A (B) means that programme B (A) cannot also be implemented. If the programmes A and B can both be implemented physically, but implementing A (B) means that the costs and effectiveness of B (A) change, then the programmes should be defined as mutually-exclusive. In this case, we have three alternatives: carrying out only A, carrying out only B, or carrying out both A and B. Mutually-exclusive programmes can be viewed as programmes for the same population, e.g. two alternative drugs for ulcer patients." (page 135)	"Two programmes, A and B, are defined as independent if the costs and effectiveness of programme A (B) are not affected by whether programme B (A) is implemented or not. The two programmes are viewed as applying to two different populations; an example would be the treatment of ulcer patients and the treatment of arthritis patients…" (page 135)	L I P
Johannesson 1997 (7)	"Two programmes are mutually-exclusive if the costs and/or effects of one programme are affected by whether the other programme is implemented or not, e.g. two alternative drug therapies to lower blood pressure."	"Two programmes are independent if the costs and effects of a programme are not affected by whether the other programme is implemented or not, e.g. a treatment for ulcer and a treatment for cancer."	I
Phillips 2009 (47)	"A distinction must be made between those interventions that are completely independent **–** that is, where the costs and effects of one intervention are not affected by the introduction or otherwise of other interventions – and those that are mutually-exclusive **–** that is, where implementing one intervention means that another cannot be implemented, or where the implementation of one intervention results in changes to the costs and effects of another."		I L
Weinstein 1996 (48)	"Comparisons among competing alternatives for the same condition. [...] the alternatives (e.g. different drugs for the same condition) are no longer independent. As an obvious example, the benefits of giving two antihypertensive drugs to the same group of patients are not additive."	"The costs and effectiveness of any programme are independent of which other programmes are adopted."	I P
WHO 2003 (15)	"Interventions are said to be mutually-exclusive if only one alternative can be selected. Mutually-exclusive interventions have also been called "competing" or "incompatible" interventions. […] Interventions are said to be independent if choosing one does not prevent the choice of any other intervention." endnote 3 "Many interventions interact in terms of either costs or effects at the population level. The health impact of undertaking two interventions together is not necessarily additive, nor are the costs of the joint production. To understand whether they are efficient uses of resources independently or in combination requires assessing their costs and health effects independently and in combination. […] Interventions that interact should be evaluated as a group […] The case of mutually exclusive options is similar, i.e. interventions which by definition cannot be implemented simultaneously in the same population. An example is population-based annual and biannual breast cancer screening. These interventions must be evaluated as part of the same set which will ensure that only one of the interventions appears in an optimal mix." pg 21		L I+

* Categories of interaction:

L: Literal definition – treatments are mutually-exclusive if patients cannot receive both.

P: Treatments for the same patient group are mutually-exclusive.

I: Treatments are mutually-exclusive if the costs or effects depend on the other treatment, although the word "interaction" is not mentioned.

I+: Interactions are mentioned in relation to mutually-exclusive treatments.

I-: Definition states that *independent* treatments may interact.