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1 Background and Objectives

An increasingly important strategy for treating many cancers is to utilise several medicines with distinct but complementary mechanisms of action in combination or in close sequence. Such regimens in use today include treatments for some forms of metastatic breast cancer, advanced melanoma, and multiple myeloma. Importantly, a review of development pipelines suggests that a strategy of combining different medicines to form combination regimens will be a mainstay of cancer treatment (IQVIA Institute, 2019).

Using medicines in combination can deliver better outcomes for patients, as shown across different tumour types and disease stages (Basraheel et al. 2020). Payers are pushing back on reimbursing them due to the total cost of providing such combination regimens (Danko et al. 2019), which stem from using multiple therapies and usually longer treatment durations as overall survival is extended. Furthermore, many HTA agencies do not find that the expected additional benefits from adding a new medicine (henceforth the add-on) to a currently reimbursed medicine (henceforth the backbone) represents value for money to the health system. Most notably, in those HTA markets that utilise cost-per-QALY approaches for assessing value, a clinically effective medicine might even be found to be "not cost-effective at zero price" when used as part of a regimen that increases treatment duration.

This counter-intuitive phenomenon of "not cost-effective at zero price" has spurred recent efforts to understand both the root causes of the problem, and what actually needs to solved for, and by whom. Importantly, it is clear, if still poorly recognised, that this is not simply a consequence of a pharmaceutical company charging too high a price for the add-on therapy. The real-world consequence of failing to solve this policy challenge is one of access, i.e. that patients may not receive a clinically superior treatment even if the pharmaceutical company were to provide the add-on medicine for free.

We postulate that this combination policy challenge arises when each of the following conditions hold:

- The expected clinical benefit of using the medicines in combination is superior to that of using either constituents as monotherapy, but the duration of treatment increases by the same amount of time as the expected increase in overall survival (OS)[1,2].
- The combination regimen comprises two or more constituent medicines that companies are expecting to be priced to value.
- These medicines are owned by two or more different companies, prohibited by competition law to negotiate with each other on the prices of individual constituents that comprise the regimen, and therefore propose an agreed total treatment cost. By way of contrast, if all constituents within the regimen are owned by a single company, that company will be able

[1] *If the increase in treatment duration for the combination over the monotherapy is less than the expected increase in OS, the add-on therapy can gain a positive price using conventional HTA approaches. There is still the important question of how best to attribute value to individual constituents, but this would not necessarily impact immediate patient access to a drug already licensed.*
[2] *There may be situations other than treatment duration increase that lead to the same problem of "not cost-effective at zero price", but we focus on treatment duration increase to illustrate the problem, while aiming for a generalisable solution.*

to present a total cost of regimen that is satisfactory to the payer and price the constituent medicines accordingly; and

- Payers are not willing to pay more per health unit gained for combination regimens than for single technology interventions. Some may make a case for payers being willing to accept this, but standard health economics methods are agnostic to the composition of costs.

When any of these conditions do not hold, then there should not be a combination policy problem to solve, at least from the perspective of providing patients access to medicines they need within typical reimbursement systems. Nonetheless, it is not uncommon that all of these conditions do in fact hold and it is likely that they will occur with increasing frequency in the future if no action is taken. Payers and pharmaceutical companies are struggling to solve a shared problem that is resulting in patients facing significant delays to access and in some cases being denied clinically superior treatments.

A recent paper by Latimer et.al (Latimer et al. 2020) discusses the proceedings of an international workshop on the topic hosted by Bellberry International. This was a broad-ranging workshop involving representatives of several major HTA agencies, patient groups, clinicians, and industry. Several core problem domains emerged, shown in Box 1.

This paper seeks to contribute to the emerging debate on this policy challenge by articulating why a new approach is required to address the *value attribution problem*. Solving this is essential, yet we stress that each of the problems requires a health system solution for the combination policy challenge to be fully resolved.

Box 1: Core problem domains in valuing and paying for combination regimens in oncology

(1) The Incentive Problem: as the value of a medicine may differ by use (monotherapy vs combination use; first line vs subsequent line, tumour type or indication etc), this difference in value will need to be reflected in the reimbursed price. Should an assessment of the value of a medicine within a combination regimen result in a price adjustment to a medicine already reimbursed in another use, there will be a strong disincentive for the owner of this medicine to renegotiate should that adjusted price flow on to all reimbursed uses of that medicine;

(2) The Value Attribution Problem: how should the value of the combination be apportioned between the constituent medicines of a regimen, and therefore how should the individual medicines be priced to reflect that value assuming a given willingness to pay for regimen itself?

(3) The Competition Law Problem: within the limits of existing competition and anti-trust law, how can competitor companies arrive at "agreed" prices for the constituent medicines within a regimen, so that the total cost of the latter is commensurate with the value of the treatment?

(4) The Implementation Problem: even if all such problems are solved, they need to be implemented within a given pricing and reimbursement system and its laws and policies. In order to solve the implementation problem, it is likely that a form of indication or multi-use pricing will be required. This is often viewed as complex, requiring separate prices for each indication or use but pragmatic approaches utilising weighted-average prices can be adopted (and indeed are in countries such as Australia.)

This paper argues that existing approaches to valuing and pricing the constituent medicines within the combination regimen require adjustment whilst remaining fully consistent with underlying health economics principles, which we take to require:

- the price of a medicine to reflect the health and health related outcomes that the medicine delivers;
- the application of standard health economic approaches, such as cost-effectiveness analysis or assessing therapeutic added value, in order to quantify the additional costs and benefits that accrue from using a combination regimen relative to the existing standard of care.

The paper develops a conceptual framework to highlight the problems posed by the current perspective for conducting an incremental cost-effectiveness analysis for a combination regimen. It uses this conceptual framework to present a critique of existing approaches to explicitly or implicitly attributing value, highlighting what we see as a naïve application of current value assessment assumptions and perspectives. This so-called naïve approach is the root cause of the "not cost-effective at zero price" phenomenon, but also underlines the challenges faced by recent efforts to attribute combination value which accept the revenue of the backbone as a given. We also explore the option to use monotherapy values when these are available. The paper concludes by setting out various criteria that any proposed solution to the Value Attribution Problem must satisfy.

2 Assumptions

In order to make the Value Attribution Problem tractable, we start by making the following (strong) assumptions. These may differ subtly or significantly from real world scenarios depending on the combination regimen under consideration and the requirements of individual reimbursement systems. Nonetheless, we maintain that they are sufficiently plausible to anchor the problem statement in a way that can help us think about a generalisable solution.

1. USE OF THE COST-PER-QALY PARADIGM

Whilst acknowledging that many important HTA agencies do not apply a cost-effectiveness approach for assessing value, we develop our conceptual framework initially in a cost-per-QALY paradigm, in the context of Cost-Effectiveness Analysis (CEA) and use of a Cost-Effectiveness Threshold (CET) which we assume is set at *k*. This is a significant simplification of such systems as we assume that incremental health gain as measured by QALYs is the only outcome that matters in terms of valuing a treatment. Thus, the value of a treatment is a linear function of the incremental health gain as measured by QALYs.

Importantly, we believe that our framework can be adapted and expressed within the conceptual frameworks that underpin the so-called "added therapeutic benefit" systems. We comment on this later in the paper.

2. STANDARD OF CARE FOR PURPOSES OF INCREMENTAL ANALYSIS

For simplicity's sake we compare combination regimens with the current monotherapy, acknowledging again that in the real world this represent only a sub-set of relevant scenarios. We further assume that the alternatives to use of the current monotherapy are either other monotherapies which are included in the combination or a standard of care (SOC) which would be used in the absence of the monotherapies included in the combination. We also assume that there are no other health system costs associated with delivering the monotherapies and combination therapies.

3. PRICING ASSUMPTIONS

We make the strong assumption that monotherapies currently in use are priced up to their threshold values, i.e. the maximum the payer is willing to reimburse. This enables us to equate the price of the treatment with the incremental value to the payer.

4. THE RELATIONSHIP BETWEEN PROGRESSION FREE SURVIVAL (PFS), TREATMENT DURATION (T) AND OVERALL SURVIVAL (OS)

The importance of changes in treatment duration to the challenge of pricing combination therapies was identified by Greber and Vaidyanathan (2014). We are looking in general at extensions in life expectancy (OS). Overall survival is the sum of the two stages Progression Free Survival (PFS) and Post Progression Survival (PPS), i.e. OS = PFS + PPS. During PFS, treatment is usually assumed to continue, but there is no treatment during PPS. One working assumption is that an increase in PFS leads to an equivalent absolute increase in OS. Payers are usually concerned that this may not be the case, with an increase in PFS not necessarily increasing OS. However, the reverse may be the case with an increase in PFS leading to an increase in post-progression survival (PPS) such that OS increases by more than the increase in PFS. To the extent that the combination adds to PPS then the balance between costs and benefits changes, as there is life gain with no additional treatment cost.

We also have the possibility that treatment duration (T) may continue for less than the full PFS stage. As more cancers become chronic rather than acute, the question as to when a combination treatment can be discontinued will become important. Of course, discontinuation is also an option for monotherapies, so the choice of treatment duration for the comparator regimen will also be important.

Quality of life (QoL) also matters. The incremental QALYs gained due to incremental PFS time and incremental PPS time may differ. The additional QoL part of the QALY gain, even during the additional PFS time, may not be at the same level as that obtained by the monotherapy, for example, using two (or more) drugs at the same time, patients may experience additional adverse (toxicity) effects. This would mean lower QoL gains and so less QALYs gained. Even if additions to OS and PFS were absolutely equivalent, the additional QALYs would not be, because of reduced QoL. In general, however, we might expect QoL to be lower in the post-progression stage. For ease of illustration we assume that QoL is the same in treatment and post treatment phases, thus OS is the only driver of health gain. We return to this issue briefly in Section 5.

We therefore start with a treatment duration (T) for the backbone therapy (T_B) (which may be ≤ PFS) and an overall survival for treatment with the backbone therapy (OS_B). The combination leads to an increase in treatment duration ΔT and an increase in OS, ΔOS. What matters, as we show formally in Appendix 1, is the relationship between $\Delta OS/\Delta T$ and OS_B/T_B. We have three possibilities:

- The ratio of the increase in OS, (ΔOS) for the combination to the increase in treatment duration (ΔT) is the same as the ratio of the treatment duration (T) for the backbone therapy (T_B) to the OS for treatment with the backbone therapy (OS_B), i.e. $\Delta OS/\Delta T = OS_B/T_B$. The proportionate relationship between the combination $OS_{(B+A)}/T_{(B+A)}$ is therefore the same as for the backbone, $OS_{(B+A)}/T_{(B+A} = OS_B/T_B$.

- The ratio of the increase in OS, (ΔOS) to the increase in treatment duration (ΔT), for the combination is less than the ratio of the (expected) OS for treatment with the backbone therapy (OS_B) to the treatment duration (T) for the backbone therapy (T_B), i.e. $\Delta OS/\Delta T < OS_B/T_B$. The proportionate relationship for the combination $OS_{(B+A)}/T_{(B+A)}$ is less than for the backbone, $OS_{(B+A)}/T_{(B+A)} < OS_B/T_B$.

- The ratio of the increase in OS, (ΔOS) to the increase in treatment duration (ΔT)for the combination is more than the ratio of the (expected) OS for treatment with the backbone therapy (OS_B) to the treatment duration (T) for the backbone therapy (T_B), i.e. $\Delta OS/\Delta T > OS_B/T_B$. The proportionate relationship for the combination $OS_{(B+A)}/T_{(B+A)}$ is more than for the backbone, $OS_{(B+A)}/T_{(B+A)} > OS_B/T_B$.

5. ASSUMING SUB-, SUPER-, OR CONSTANT ADDITIVE SCALE OF THE HEALTH GAIN FROM THE COMBINATION

We introduce the terms Sub-, Super-, or Constant Additive Scale[3] of the combination to make an important distinction as to how much additional value is generated (in terms of the incremental gain in health) by combining a backbone therapy, drug B, and an add-on therapy, drug A and in terms of the health gain, H, when compared with their independent use (as monotherapies). We term the incremental health gain over SOC of their use in monotherapy as H(B) and H(A) respectively, and the

[3] *We introduce this new terminology because we are not aware of any applicable economic terms in the existing literature. For example, diminishing returns is not relevant. We do not have a fixed input, as both inputs vary. Returns to scale is not relevant as we do not have proportionate increases in the inputs. We move from use of one of two inputs that are imperfect substitutes producing different quantities of outcome to a combination of the two inputs which produces a greater quantity of outcomes.*

incremental health gain over SOC from their use in combination as H(B+A). Of course, the add-on therapy (drug A) may be new and not have evidence of its value as a monotherapy, in which case we have only partial information about its value as a monotherapy, and hence of the underlying additive scale. We comment on this possibility later.

There are three possible additive scale scenarios which we interpret as follows:

(i) Constant Additive Scale (CAS): In this situation H(B) + H(A) = H(B+A). For example, assume the backbone (B) generates 1 additional year of OS and the value of the add-on (A), if it were to be given as a monotherapy, would be to add 0.5 years of OS. Hence B is preferred as a monotherapy. However, we find that B+A given as combination therapy, adds 1.5 years of OS. So we have H(B) [=1] + H(A) [=0.5] = H(B+A) [=1.5].

(ii) Sub-additive Scale (SubAS): In this situation H(B) + H(A) > H(B+A). As above, we assume the backbone therapy B generates 1 additional year of OS and the value of the add-on therapy A, if it were to be given as a monotherapy, would be to add 0.5 years of OS (hence B is preferred as a monotherapy). However, B+A given as combination therapy, adds 1.2 years of OS, i.e. H(B) [=1] + H(A) [=0.5] > H(B+A)[=1.2].

(iii) Super-additive Scale (SuperAS): In this situation H(B) + H(A) < H(B+A). As above we assume the backbone therapy B generates 1 additional year of OS and the value of the add-on therapy A, if it were to be given as a monotherapy, would be to add 0.5 years of OS (hence B is preferred as a monotherapy). However, B+A given as combination therapy, adds 2 years of OS, i.e. H(B) [=1] + H(A) [=0.5] < H(B+A)[=2].

We can illustrate these in Figure 1 below. The yellow and green bars show the incremental health gain of treatment B =1 and A = 0.5 respectively. The blue bars show the three possible additive scale scenarios with (i) H(B+A) =1.5 (constant additivity); (ii) H(B+A) =1.2 (sub additivity); and (iii) H(B+A) = 2 (super-additivity).

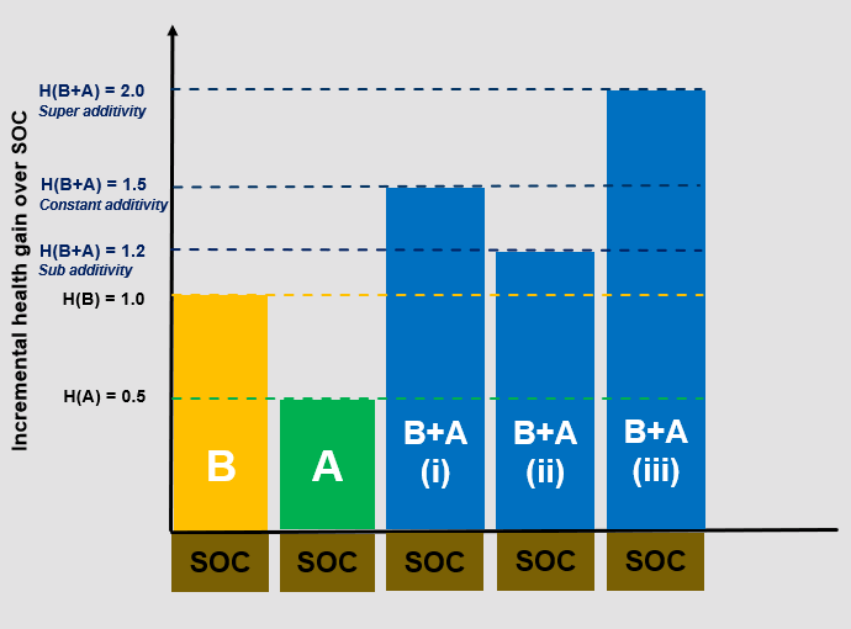

FIGURE 1: ILLUSTRATION OF CONSTANT / SUB- / SUPER- ADDITIVITY
Key: B=backbone treatment, A=add-on treatment, SOC = standard of care

The estimate of the health gain of the add-on therapy is defined by the incremental health gains of the combination versus the monotherapy. Note that we show SOC below the x axis for illustration. As set out in the assumptions above, we assume that the alternatives to use of the current monotherapy are either other monotherapies which are included in the combination, or a SOC. Our analyses focuses on the incremental health outcomes for the monotherapies and combination therapy over the SOC outcomes. We also assume that there are no other health system costs associated with delivering the monotherapies and combination regimens. This enables us to focus on a comparison of the value attribution as between B and A under different assumptions.

In the next two sections we use this conceptual framework to analyse the problems with current approaches to the use of value assessment of combination regimens and issues with two proposals that have been made in the literature. We show that two drivers: (1) the relationship between progression free survival (PFS), treatment duration (T) and overall survival (OS); and (2) the sub-, super-, or constant additive scale of the health gain from the combination are both important to understanding the nature of the challenge of current and proposed approaches, albeit in very different ways.

3 Current Approaches to Value Assessment in Combination Pricing

The current payer and HTA body approach to valuing combination therapy is to assume that the price of the backbone therapy is a given. The impact of this approach on the value-for-money of the combination depends on a number of factors, but in particular on the relationship between the change in treatment duration and the change in overall survival. We set out in Table 1 a summary of the potential impact of different assumptions. The supporting equations are set out in Appendix 1.

Note that OS/T is impacted by treatment duration, which under current combination pricing rules involves the backbone continuing at its current price. Thus, under current approaches to valuing combinations, we can see the impact of the price of the add-on therapy on the cost-effectiveness of the combination depends on the relationship between T and OS. Recapping the three possibilties we set out in Section 2 above in the context of the current approach to value assessment:

- If $\Delta OS/\Delta T = OS_B/T_B$ then the combination therapy can be cost-effective under current rules as extending use of the backbone therapy at its existing (just cost-effective monotherapy) price will work as the ratio of the increase in the period of OS to the period of increased treatment is unchanged. However, there is no headroom to price the add-on therapy above zero. If the add-on has a positive price, the combination will not be cost effective.

- If $\Delta OS/\Delta T < OS_B/T_B$ then extending use of the backbone therapy as part of the combination usage at its existing (monotherapy) price will itself render the combination not cost-effective as the ratio of the period of increased OS to the increase in the period of treatment is less than the ratio for the background therapy. Thus, when the costs of the additional use of the background therapy are added to the existing costs, there will be no price (other than a negative one) at which the add-on therapy can be set and the combination found to be cost-effective.

- If $\Delta OS/\Delta T > OS_B/T_B$ then there is room for the add-on therapy to be priced above zero and for the combination to be cost-effective under the current approach. How much room will depend on the extent to which the ratio of increase in OS to increase the period of treatment ($\Delta OS/\Delta T$) exceeds the current ratio OS_B/T_B.

TABLE 1: IMPACT OF CHANGE IN TREATMENT DURATION RELATIVE TO OVERALL SURVIVAL ON THE DEGREE OF PRICING CHALLENGE FOR A COMBINATION THERAPY UNDER CURRENT HTA APPROACHES

Relationship between change in overall survival ΔOS and in treatment duration ΔT change, as a result of the combination	$\Delta OS/\Delta T = OS_B/T_B$ and therefore $OS_{B+A}/T_{B+A} = OS_B/T_B$	$\Delta OS/\Delta T < OS_B/T_B$ and therefore $OS_{B+A}/T_{B+A} < OS_B/T_B$	$\Delta OS/\Delta T > OS_B/T_B$ and therefore $OS_{B+A}/T_{B+A} > OS_B/T_B$
Consequences for the cost-effectiveness of the combination	Combination only cost-effective at zero price of add-on	Combination not cost effective at zero price for add-on.	Scope for the combination to be cost-effective with add-on therapy price above zero
Combination cost-effective under current rules if the add-on therapy has a price >0	No	No	Possibly

Thus we can see that in the current incremental cost-per-QALY value assessment framework, a significant proportion of combinations of on-patent products (comprising a "backbone" therapy and an "add-on" therapy) are not cost-effective. If the combination therapy increases treatment duration the cost associated with the backbone therapy extends to the added life years. In these circumstances, if $\Delta T \geq \Delta OS$ and if there are any other additional costs associated with administering the combination over and above administering the monotherapy, then we have the much commented upon result (Davis et al. 2014) that the combination will not be cost-effective even if the added product is priced at zero. If on the other hand, $\Delta T < \Delta OS$ (at the limit $\Delta T_B = 0$) then it is possible that there is room for the combination be cost-effective with A getting a positive price[4].

Under the current value assessment approach, the implied value attribution for the add-on will be a residual of the value of the combination V(B+A) = k*H(B+A) minus any incremental cost of the backbone therapy as part of the combination extended OS. We can illustrate the effect of this in Figure 2 below. Note that the y axis is now *value* rather than health (and under our assumption V=*k**H), in order to illustrate how payments for the backbone therapy B can eat into the residual value attributable to A. Also, for simplicity, recall that me have assumed that all of the gain in health is assumed to arise from an increase in OS at constant QoL.

[4] *Strictly, as we show in Appendix 1, and describe above, it is the relative size of the ratios of the extended period of OS to that of T ($\Delta OS/\Delta T$) to the existing ratio OS_B/T_B that matters. However, if we assume that $OS_B > T_B$ (there is some period of post progression survival in which the patient does not receive treatment) then if $\Delta T \geq \Delta OS$, the condition $\Delta OS/\Delta T < OS_B/T_B$ holds and A will be not cost-effective at zero price. Conversely, if $\Delta T = 0$ then the condition $\Delta OS/\Delta T > OS_B/T_B$ holds and it is possible that A can get a positive price and the combination be cost-effective. It is necessary for $\Delta T < \Delta OS$ for A to get a positive price but not sufficient. What matters is whether the amount by which $\Delta T < \Delta OS$ is sufficient for the condition $OS_{B+A}/T_{B+A} > OS_B/T_B$ to be met.*

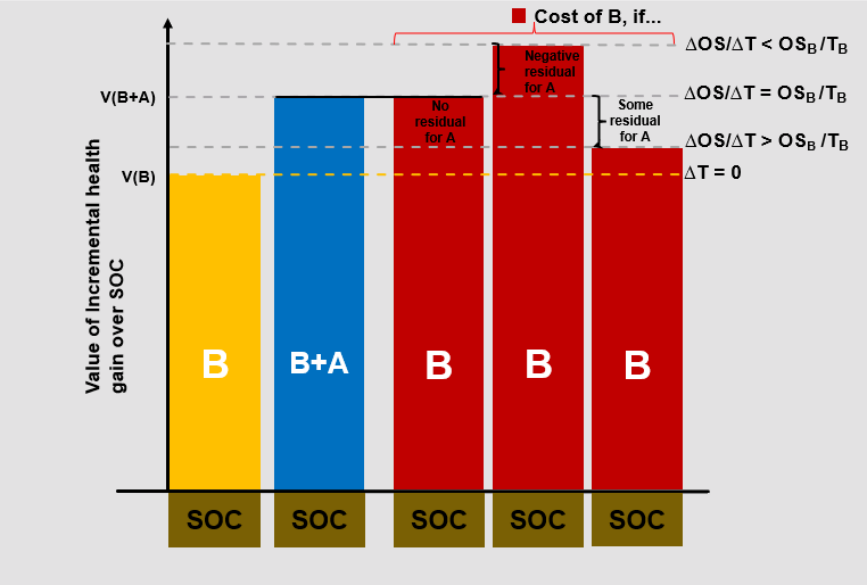

FIGURE 2: THE IMPACT OF TREATMENT DURATION RELATIVE TO OVERALL SURVIVAL WHEN THE PRICE OF THE BACKBONE THERAPY IS UNCHANGED IN THE COMBINATION REGIMEN

We illustrate that:

- if $\Delta OS/\Delta T = OS_B/T_B$, then it is cost effective at zero price for A, (i.e. no residual) and
- if $\Delta OS/\Delta T < OS_B/T_B$, then payments for therapy B take up more than all of the value generated by the combination, so it is not cost-effective at zero price for A (negative residual value).
- if $\Delta OS/\Delta T > OS_B/T_B$, then there will be some residual value for A.

Note that the factor impacting whether or not A can get a positive price if the backbone treatment gets an unchanged price in combination use is the first of the two drivers we highlighted in Section 2, i.e. the relationship between progression free survival (PFS), treatment duration (T) and overall survival (OS). In the next section we discuss approaches to value attribution which do not make the assumption that the backbone treatment gets an unchanged price in combination use. In these circumstances it is the second of our two drivers - the sub-, super-, or constant additive scale of the health gain from the combination – which is the key determinant of value attribution.

4 Proposed Approaches to Combination Value Attribution

The (little) literature we have identified (Danko et al. 2019; Humphrey et al. 2011; Persson and Norlin 2018; and for a review see Latimer and Pollard, 2019), has argued that the price of the (backbone) monotherapy needs to be revisited, but no clear approach has been offered about how this should be done, and in particular how value should be attributed between the specific constituent products in the combination. Where approaches have been offered, these seem to assume companies are bargaining on a product by product, country by country, basis and use a value attribution approach that takes as a starting point the assumption that the maximum value of the add-on is the additional value it brings in combination as compared to the value provided by the backbone therapy. In other words, the value of the backbone therapy in its monotherapy use is taken as a given and the revenues gained by the product in that use as an irreducible minimum. This is because it is assumed that there is no incentive for the owner of the backbone to bargain over price if they do not receive at least their current revenues. Proposals therefore offer to provide only the incremental value/cost of the combination to the add-on therapy. How much this is depends on:

- the pricing policy proposed for the backbone therapy, which can range from (i) capping the costs of the backbone therapy, i.e. the backbone therapy for any extended survival is effectively provided free of charge, to (ii) allowing the backbone therapy to maintain its existing price for the extended duration of the combination treatment regimen; and
- the two key drivers we have identified:
    - the underlying additivity of the combination;
    - the length of time the backbone treatment extends for.

There is an implicit assumption in this literature that the outcome achieved by the add-on therapy in monotherapy use is not known, and that we are seeking a solution to a problem of partial information. We know the value of the backbone therapy as monotherapy, but not that of the add-on as a monotherapy. An alternative basis for this approach could be, however, that the value of A as a monotherapy is known but B is the better monotherapy and has "squatters rights", so the working assumption is that A has to take what is left after B has been paid, a pricing policy is imposed, or agreement is reached between the owners of B and the owners of A.

An alternative approach to this was put forward for consideration by Briggs (2020). This is when the outcome of using the add-on as a monotherapy is known (i.e. we have full information) and is to attribute value in the combination regimen in the ratio of the value of each component of the combination regime the used as a monotherapy.

In the following, we will explore two approaches to value attribution:

1) A partial information scenario, with no outcomes data for the add-on therapy in monotherapy use available, which we term the "partial information incremental value attribution approach", and

2) A full information scenario, with monotherapy outcomes data available for each component of the combination, which we term the "full information monotherapy ratio approach".

Importantly both of these value attribution approaches require a price change for the backbone (and for the add-on, if the add-on is already available and priced on the market) when used in a combination regimen. This will be needed to ensure that the individual treatment cost of backbone and add-on in combination use is matching the attributed value for each therapy. This will ensure that the total combination cost corresponds to the overall combination value.

In the following analysis we let $V_a(B)$ and $V_a(A)$ denote the value attribution shares of the total (incremental) value of the combination $V(B+A) = k\ H(B+A)$, with $V_a(B) + V_a(A) = 1$[5].

4.1 Partial Information Incremental Outcomes Value Attribution Approach

The available outcomes data under a partial information scenario is illustrated in Figure 3 below. In this scenario, the add-on therapy is attributed the full incremental health gains of the combination versus the backbone monotherapy given. This is $\Delta H(B+A) = H(A+B)-H(B)$.

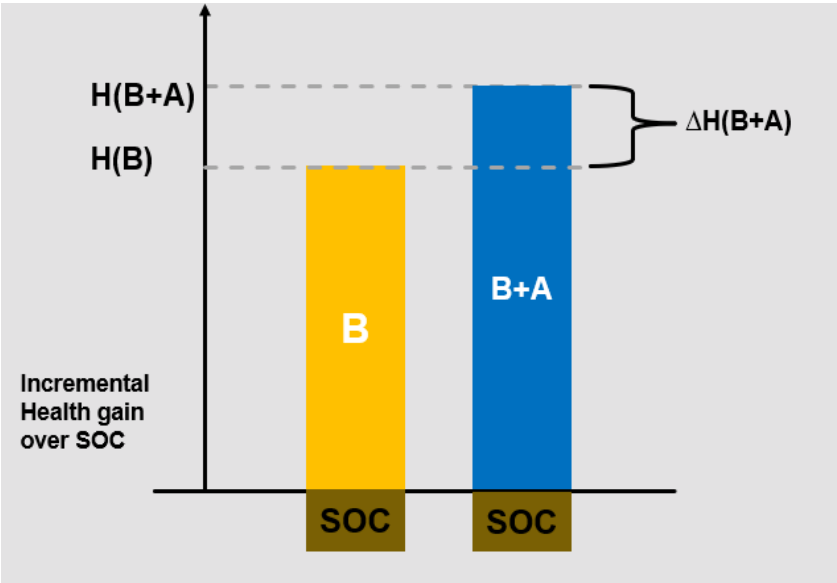

FIGURE 3: PARTIAL OUTCOMES INFORMATION SCENARIO

Based on this, the proposed value attribution for the add-on therapy A is given by the incremental combination outcome proportion relative to the overall combination outcomes, ie $V_a(A) = \Delta H(B+A)/H(B+A)$. The value attribution for the backbone therapy is correspondingly given by the proportion of the backbone monotherapy outcome relative to the combination outcome, ie $V_a(B) = H(B)/H(A+B)$.

Under this approach backbone therapy attains its value and cost from the monotherapy use (with cost capped at the monotherapy cost level) and the add-on therapy is attributed the value of the incremental combination outcomes.

[5] *Note that we now analyse value attribution shares, rather than the health gain that might be attributed to each product in the combination regimen. Because value (and price) is a linear function k of health gain, these attribution shares of the value of the combination regimen can be readily turned into expected revenues for products B and A.*

To illustrate resulting value attributions let us assume that (say) H(B) = 7 QALYs, and H(B+A) = 9 QALYs. The assumed incremental health outcome contribution of A to the health outcome of the combination is therefore 2 QALYs. The relative shares of the total value will be $V_{a,}$ (B)= H(B) / H(B+A) and V_a (A) = ΔH(B+A) / H(B+A) and reflect the 7/9 and 2/9 relationship for backbone and add-on respectively as the value attributed to each constituent combination therapy out of the total combination value *k** H(B+A)=*k**9.

4.2 Full Information Monotherapy Outcomes Ratio Value Attribution

The scenario where we know backbone and add-on therapy outcomes in monotherapy use is illustrated in Figure 4.

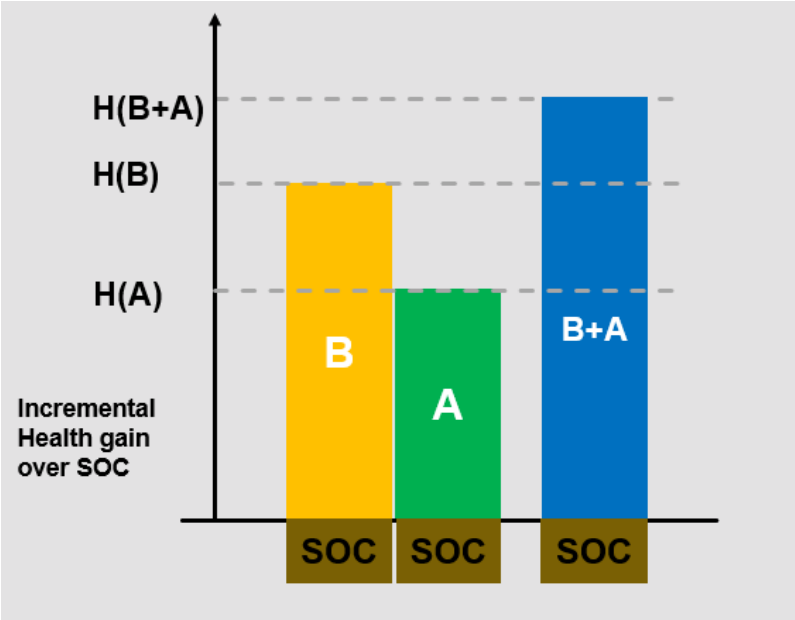

FIGURE 4: FULL OUTCOMES INFORMATION SCENARIO

Briggs (2020) identified one possible value attribution method in the full information scenario. This is to recognise the importance of both products in contributing to the value of the combination therapy by defining the value attribution for each component by the simple ratio of the of the monotherapy outcomes to the sum of their respective monotherapy values. Using our example with H(A+B) = 9 QALYs and H(B) = 7 QALYs and for illustration let us assume that H(A) = 5 QALYs, the value attribution for backbone is V_a (B) = H(B)/(H(A)+H(B)) = 7/12 = 0.583, and for add-on V_a (A) = H(A)/(H(A)+H(B)) = 5/12 = 0.417.

Note that the assumption we are making here about the cost of B is much stronger than the assumption made in the partial information scenario where the backbone attained its monotherapy value and cost. In the full information scenario, the cost of the backbone therapy in the combination regimen is completely flexible and determined by the attribution method. In the example above, B is valued in monotherapy use at V(B) = *k**7. However, as part of the regimen it is valued at V(B) = *k**0.583*9, which is much less. This is because we have a case of sub-additive scale, where the value of the combination is worth less than the sum of the value of the two treatments when each is used as a monotherapy.

4.3 Comparing the Incremental (Partial Information) and the Monotherapy Ratio (Full Information) Approaches

We set out in Table 2 below a comparison of the two approaches for our SubAS example illustrated above with backbone H(B) = 7, and add-on H(A) = 5, and the combined health gain H(A+B) = 9. The sum of the monotherapy health gains H(B)+H(A) = 12. This is Case 1. We also include another example, Case 2, with the same values for backbone H(B) = 7 and the combined health gain H(A+B) = 9, but with add-on H(A) = 3. In Case 2, the sum of the monotherapy health gains H(B)+H(A) = 10.

In this example we have a case of SubAS, and it can be seen, in Case 1, that the full information monotherapy ratio approach is attributing more value share to the add-on therapy (0.417) (and less to the backbone 0.583) compared with the partial information incremental value attribution approach discussed above which gives a value share of 0.222 to the add-on and 0.778 to the backbone. In Case 2 the full information monotherapy ratio approach is also attributing more value share to the add-on therapy (0.300) (and less to the backbone 0.700 compared with the partial information incremental value attribution approach which, as in Case 1, gives a value share of 0.222 to the add-on and 0.778 to the backbone. The differences between the two approaches is less because the degree of sub-additivity is less in Case 2, i.e. the benefits of the sum of the two monotherapies is closer to the value of the combination as compared to Case 1. In the limiting case we have constant additive scale when the sum of the two monotherapies is equal to the value of the combination and the two approaches will give the same answer. We discuss a CAS example later in this section.

The overall effect is, however, clear in both Case 1 and Case 2. The add-on creates more incremental value against the SOC as a monotherapy than it does as an add-on to the current preferred monotherapy B, thus the monotherapy ratio approach gives the add-on therapy a larger share of the value of the combination regimen than the partial information incremental value attribution approach.

TABLE 2 SUB-ADDITIVITY EXAMPLES WITH ALTERNATIVE ATTRIBUTION APPROACHES

	Sub-add	Incr. ratio	Mono ratio	Ratio of mono to incr.	Sub-add	Incr. ratio	Mono ratio	Ratio of mono to incr.
	Case 1				*Case 2*			
Backbone H(B)	7	0.778	0.583	0.750	7	0.778	0.700	0.900
Add-on H(A)	5	0.222	0.417	1.875	3	0.222	0.300	1.350
Combo H(A+B)	9				9			
Sum of mono H(B)+H(A)	12				10			

Key: incr. = incremental.

We now use the same two case studies but create a scenario of SuperAS, where the combined health gain H(A+B) = 15.

TABLE 3 SUPER- ADDITIVITY EXAMPLES WITH ALTERNATIVE ATTRIBUTION APPROACHES

	Super-add	Incr. ratio	Mono ratio	Ratio of mono to incr.	Super-add	Incr. ratio	Mono ratio	Ratio of mono to incr.
	Case 1				*Case 2*			
Backbone H(B)	7	0.467	0.583	1.250	7	0.467	0.700	1.500
Add-on H(A)	5	0.533	0.417	0.781	3	0.533	0.300	0.563
Combo H(A+B)	15				15			
Sum of mono H(B)+H(A)	12				10			

Key: incr. = incremental

We can see that in the scenario of SuperAS, the reverse occurs in both Cases 1 and 2. The add-on creates more incremental value against the SOC as an add-on to the current preferred monotherapy B, than it does as a monotherapy, thus the partial information incremental value attribution approach gives the add-on therapy a larger share of the value of the combination regimen than the monotherapy ratio approach.

We can see that the monotherapy ratio value attribution shares are the same in Cases 1 and 2 and the same as in Scenario 1 of sub-additivity because these shares do not depend at all on the absolute health gain achieved by the combination regimen. However, the partial information incremental value attribution approach does depend on the absolute health gain, which is higher in the SuperAS Scenario 2 at 15 QALYs as compared to 9 QALYs in the SubAS Scenario 1. In the SuperAS case 0.533 of the value under the incremental approach goes to the add-on therapy as compared to 0.222 in the SubAS Scenario 1 example.

The validity of the partial information incremental value attribution approach depends crucially on the applicable additive scale scenario for the combination being assessed. In our view the evidence indicates that SubAS is likely to be the norm. Under this scenario H(B) + H(A) > H(B+A), or equivalently H(A) > H(B+A)-H(B). In other words, the non-observed missing monotherapy outcome for the add-on therapy is likely to be bigger than the incremental outcome added to the outcomes of the combination. Based on this, the use of the incremental approach would provide a lower boundary of the appropriate value attribution and likely undervalue the add-on therapy, with important consequences for the incentive to innovate.

Conversely, if we did have a case of SuperAS, when H(A) < H(B+A)- H(B) the use of the incremental approach would provide an *upper* boundary of the appropriate value attribution and likely overvalue the add-on therapy. Only in the special case of CAS will the two valuation approaches (the

incremental approach and the monotherapy ratio approach) be the same. For completeness we show this in Table 4 below.

TABLE 4: CONSTANT- ADDITIVITY EXAMPLES WITH ALTERNATIVE ATTRIBUTION APPROACHES

	Super-add	Incr. ratio	Mono ratio	Ratio of incr. to mono	Super-add	Incr. ratio	Mono ratio	Ratio of mono to incr.
	Case 1				*Case 2*			
Backbone H(B)	7	0.583	0.583	1.000	7	0.700	0.700	1.000
Add-on H(A)	5	0.417	0.417	1.000	3	0.300	0.300	1.000
Combo H(A+B)	12				10			
Sum of mono H(B)+H(A)	12				10			

Key: incr. = incremental

One important issue with the incremental approach is that it gives a different value attribution depending on which product is used as monotherapy. The only situation where the sequence order does not matter is, again, if constant additive scale (CAS) holds. In any other situation, B added to A will give a different value attribution with current HTA approaches than A added to B. To illustrate this, let us take our first example where we assume that monotherapy trials of H(A) found it generated an incremental 5 QALYs over SOC. This was not enough to displace monotherapy B with its superior 7 QALYs. Given the combination regimen generates 9 QALYs, the incremental approach gives us a value for A of V(A) = *k**(0.222*9) = *k**2. However, if A had come first and B had not been trialled in monotherapy then A would have retained its monotherapy value V(A) = *k**5, leaving V(B) = *k**4, i.e. *k**(9-5). Sequence matters. In our view an acceptable estimation method requires the value of A in (A+B) to be the same as the value of A in (B+A), as the clinical regimen (A+B) is identical to (B+A) in terms of the value it delivers. Thus, the incremental approach with partial information is not offering a generally valid method to define value attribution.

Comparing the two approaches, the following general results hold under different additive scale assumptions:

- With SubAS, H(B+A) < H(A)+H(B) which implies that monotherapy ratio V_a (B) < incremental V_a (B), and correspondingly monotherapy ratio V_a (A) > incremental V_a (A)
- With CAS, H(B+A) = H(A)+H(B) which implies that monotherapy ratio V_a (B) = incremental V_a (B), and correspondingly monotherapy ratio V_a (A) = incremental V_a (A)
- SuperAS, H(B+A) > H(A)+H(B) which implies that monotherapy ratio V_a (B) > incremental V_a (B), and correspondingly monotherapy ratio V_a (A) < incremental V_a (A)

One major argument against the potential relevance and validity of the proposed monotherapy ratio value attribution under full information is the fact that the attribution is solely based on the individual monotherapy outcomes and does not take the actual combination outcome into account. Only under the restrictive and highly unlikely scenario of CAS is the sum of individual outcomes (H(A)+H(B) the same as the combination regimen outcomes. Only under this specific condition are the partial (incremental) and full information (monotherapy ratio) approaches equivalent.

A requirement of any proposed value attribution approach is that it should produce plausible and reasonable attribution of value regardless of the applicable additive scale scenario. Case 2 in Table 3 with super-additivity shows the add-on therapy only getting 30% of the value in the case of the monotherapy ratio approach yet 53% of with the incremental approach. In the extreme, let us suppose a case in which the add-on therapy has no value as a monotherapy, i.e. H(A)=0. If we keep H(B+A)=15, and H(B) = 7, then the proposed full information monotherapy ratio value attribution (taking no account of the combination outcomes) would in this case attribute 100% of the overall combination value (V(B+A)= *k**15) to the backbone ($V_{a,}$(B) = 7/(0+7) = 1) and 0% to the add-on, despite the significant incremental combination outcomes over backbone that is only possible thanks to the combination itself, and not because of the backbone alone.

This may be an extreme example, but it illustrates an important shortcoming of monotherapy ratio-based value attribution that should lead to important questioning of the general validity of this proposed approach.

To summarize, we have illustrated two approaches that can easily be applied in the partial and full information scenarios, one of which provides a lower bound (and potentially undervalues) the value attribution of the add-on therapy in the (in our view most likely) situation of SubAS, the other which lacks any anchoring to actual combination outcomes and hence may lead to implausible results.

5 Applicability Beyond a Simplified Cost-Per-QALY System

For ease of development and explanation we have set out the problem using the example of a simple cost-per-QALY based HTA system, and two products. However, the problem is a general one, and the outcomes do not have to be QALYs translated into value by a constant factor *k*. The vertical axes in our figures can reflect any outcome measure deemed appropriate by the payer or HTA body acting on its behalf. Likewise, the translation of those outcomes into value or an acceptable price for the combination or part thereof, can use any approach, including therapeutic added value, whereby clinical benefit is translated into price. In reality, as we have noted, quality of life can vary in the treatment and post-treatment phases. Although it makes the calculations more complex, this can be handled in our analysis. The point remains that the challenges are the same whichever valuation system is used and however complex the impact of a treatment combination is on the quality and quantity of life, or on any other outcomes that are important to payers.

6 Discussion

To contribute to the emerging debate on why a new approach is required to address the value attribution problem in combination treatments, we have set out two key concepts required for an understanding of the relative performance of a combination regimen as compared to a monotherapy, considering (i) additive scale and (ii) the relative change in treatment duration as compared to the increase in OS. We have illustrated how current HTA approaches, which we characterise as naïve, lead in many cases to the add-on therapy not being cost-effective even at zero price. We term it naïve because it does not get to the root cause of understanding the issue. This is, quite simply, that most combinations have sub-additive scale, have an increase in treatment duration relative to OS that is at least proportional to that of the monotherapy, and the HTA approaches assume the backbone therapy is able to maintain its price in the new combination regimen indication.

Our conceptual framework shows that the two new approaches – the partial information incremental value approach, and the full information monotherapy ratio approach are only comparable if we make an implicit assumption of CAS. However, in practice it likely is that SubAS is the norm, *in which case using the incremental approach means the add-on therapy is undervalued relative to the backbone therapy*. Of course, if we have SuperAS, then A is being overvalued by this incremental approach. The monotherapy ratio approach values the add-on independently of its contribution to the combination regimen, i.e. whether we have SubAS, CAS, or SuperAS. This is a fundamental weakness. In the extreme, if A has no value as a monotherapy but creates a SuperAS combination, the monotherapy ratio approach would give a value of zero to A, and give all of the extra value to B.

The monotherapy ratio approach could also be criticised for relying on knowing the monotherapy value of A. Our view is that it should be possible to estimate monotherapy outcomes data for the add-on therapy A when evidence is not available from trials of A as a monotherapy by using a Bayesian approach to estimate the expected outcomes of the constituent part for which there is no data (Briggs, 2006).

Overall, we need an approach that is able to combine the best features of the two approaches we set out, i.e. it recognises the contribution of each product as a monotherapy, and also recognises their respective contributions to the combination regimen.

7 General Principles and Policy Implications

This brings us to the issue of what general principles we might expect an attribution mechanism to meet. Our starting point is that there is an underlying true and invariant contribution that A makes to the value of the combination (A+B), and an underlying true and invariant contribution that B makes to the value of the combination (A+B). These true underlying values[6] are independent of us observing, measuring, or assigning specific values to them[7].

Our thinking is that principles for generalisability could include satisfying the following conditions:

- Universal: the solution provides principles that allow value attribution for most possible configurations of combination therapy. These configurations include:
    - differing amounts of health gain provided by the combination in relation to the sum of the monotherapies. If, for example, treatment A provides 1 unit of benefit as a monotherapy and treatment B provides 1 unit of benefit as a monotherapy, the solution works if the combination (A+B) provides 2 units, < 2 units, or > 2 units of benefit;
    - the presence of either full or partial information about the value of the component parts of the combination therapy as monotherapy treatment. Handling the (most common) scenario of partial information will be key to developing a generalisable framework and further research is needed in this area;
    - combinations of two and more than two on-patent drugs in the combination regimen;
    - HTA systems that use different measures of health gain to assess value and therefore price (i.e. for QALY or non-QALY based therapeutic added value systems);
    - both similar and differential impact on PFS and OS, and on treatment duration relative to both.
- Logical and symmetric: the proposal is neutral as between all constituents of the combination, regardless of who is the backbone or the add-on. The order of backbone vs add-on sequence is not impacting the value attribution between the combination constituents. No product is "first" in the combination. By definition, the combination is only created at the point at which all of the component parts are present. It therefore follows that the value of A in (A+B) must be the same as the value of A in (B+A) as the clinical regimen (A+B) is identical to (B+A) in terms of the value it delivers. It then follows that approaches to estimating relative contributions that assign a value to either A or B with (A+B) but do not assign identical values to A and B with (B+A) are a priori illogical and not producing a correct estimate of the underlying contributions of the two products.
- Complete: the proposal will always produce an attribution of the full value of the combination between the component parts.

[6] *Value is used here as a generic term. It may refer to clinical benefit, to cost-effectiveness, or to any metric chosen to represent value in a specific environment.*
[7] *Even if the reader doesn't accept the starting point of there being a true and invariant underlying value of each constituent to the combination, we hope that they would accept the need for value attribution rules that are universal, logical, symmetrical and complete.*

In public policy terms, it is in our view essential that HTA bodies and / or payers involve themselves in the development of an attribution framework. This will be particularly important where the translation of clinical or health effect or other outcome measure is not readily transferable into value and therefore price.

A solution to the Value Attribution Problem is also critical for solving the broader Combination Regimen Policy Challenge as described earlier. We have set out criteria to be met in order for any value attribution framework to be valid based on a root cause analysis of the "not-cost effective at zero price" phenomenon and by highlighting the problems posed by the proposed approaches we have identified in the literature to assigning value and therefore a price to an add-on medicine within a combination regimen.

While a solution to the Value Attribution Problem will not in itself fully resolve the broader policy challenge, it is, in our view, a critical prerequisite for solving the other problems, including the Competition Law Problem and notably the Incentive Problem. The latter will, in many markets, require the adoption of some form of indication or multi-use pricing. A valid value attribution process will itself help to enable this.

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APPENDIX 1: IMPACT OF CHANGE IN TREATMENT DURATION ON VALUING ADD-ON PRODUCTS WITH CURRENT HTA APPROACHES.

Note that we are making the simplifying assumption that the quality of life element of the QALYs associated with changes in OS are the same regardless of whether the increase in OS occurs in the PFS or PPS stages of the disease. It is possible to incorporate different quality of life contributions in PFS and PPS components as OS=PFS+PPS, so OS (QALYs) = QoL(PFS)*PFS+ PFS+ QoL(PPS)*PPS. However, this complicates the essential point we want to illustrate.

When the treatment duration (T) changes, the T/OS ratio is critically important in determining whether existing HTA approaches can reward the add-on product A.

SCENARIO 1: TREATMENT WITH BACKBONE MONOTHERAPY PRODUCT B

We assume the price has been set such that the cost per patient of the drug over the treatment period (T) is equal to its QALY gain * threshold WTP (*k*)

Let us also assume the treatment period is measured in months.

$C_B = k*QALY_B = k*QoL*OS_B$

Cost per T (ie cost per month in treatment): $C_B/T_B = (k*QoL*OS_B)/T_B$

Thus $C_B = [(k*QoL*OS_B)/T_B]* T_B$

We can note that the cost per patient of the drug is equivalent to the revenues per patient received for drug B, which we call R_B1, i.e. revenues per patient received by drug B in scenario 1. So $R_B1 = C_B$

SCENARIO 2: TREATMENT WITH COMBINATION THERAPY OF BACKBONE PRODUCT B PLUS ADD-ON THERAPY A

Adding A to B gives, for the combination B+A:

Total regimen B&A cost:

$C_{B+A}=C_B+\Delta C= k(QoL*OS_{B+A})$

Assume QoL is unchanged, OS is the only variable

$C_{B+A}=C_B+\Delta C= k*QoL*(OS_{B+A}) = k*QoL*(OS_B + \Delta OS)$

$\Delta C = C_{B+A} - C_B = k*QoL*(\Delta OS)$

Cost per T (ie cost per month in treatment): $C_{B+A}/T_{B+A} = k*QoL*(OS_{B+A})/T_{B+A}$

Thus $C_{B+A}=[k*QoL*(OS_{B+A}))/T_{B\&A}] * T_{B+A})$

Note that $\Delta T = T_{B+A} - T_B$

$\Delta C/ \Delta T = k*QoL*(\Delta OS)/ \Delta T$

Is there any increase in value in a conventional HTA process not taken up by product B at its existing price?

Comparing cost per T for B+A vs B:

We assume the price of B is unchanged so cost and equivalent revenues for drug B in Scenario 2 (which we call R_B2) are now part of the combination and given by the cost in monotherapy plus the cost of B in the additional treatment period.

$R_B2 = C_B + [k*QoL*OS_B /T_B] * \Delta T$

Overall costs are $C_{B+A}=C_B+\Delta C = C_B + k*QoL*(\Delta OS)$

Based on this, the cost (and equivalent revenue) for drug A is given by the residual of the total threshold cost for the combination minus the backbone therapy cost as part of the combination.

$R_A2 = C_{B\&A} - R_B2$

$R_A2 = C_B + k*QoL*(\Delta OS) - C_B - [k*QoL*OS_B /T_B] * \Delta T$

$R_A2 = k*QoL*[\Delta OS – (OS_B /T_B)*\Delta T]$

For $R_A2 > 0$, then $\Delta OS > (OS_B / T_B)*\Delta T$, i.e. $\Delta OS/\Delta T > (OS_B / T_B)$

If $R_A2 = 0$ then, $\Delta OS = (OS_B / T_B)*\Delta T$, i.e. $\Delta OS/\Delta T = (OS_B / T_B)$

and for $R_A2 < 0$, then $\Delta OS < (OS_B / T_B)*\Delta T$, i.e. $\Delta OS/\Delta T < (OS_B / T_B)$

So for drug A to have a price that is +ve / 0 / -ve

then $\Delta OS/\Delta T > / = / < OS_B / T_B$

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