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Proposal for a General Outcome-based Value Attribution Framework for Combination Therapies

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Table of Contents

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1 Background, Objectives, and Criteria for Success

An increasingly common strategy for treating many cancers is to utilise several medicines with distinct but complementary mechanisms of action in combination or in close sequence (IQVIA, 2019; Bashraheel et al, 2020). Valuing and pricing the components of a combination therapy gives rise to several challenges for companies, payers and HTA bodies particularly when two or more of the products in combination are owned by different companies, each of which seeking a value-based price for their product (Davis, 2014; Greber et al. 2014; Person et al. 2018; Danko et al. 2019). These challenges have been discussed in a number of places (Latimer et al. 2019, Latimer et al. 2020; Latimer et al 2021a; Latimer et al 2021b; Briggs et al. 2020, Briggs et al., 2021) and include (1) competition law issues, which prevent companies from discussing prices with each other, (2) the challenges of implementing different prices for the same product in different uses (for example as a monotherapy and in a particular combination use), and (3) how to attribute value between products in a way that incentivises appropriate innovation, i.e. the development of treatments that can address patient need at prices that represent value for money for health care systems. A consequence of those challenges remaining unaddressed is that effective combination treatments may not be reimbursed, with patients not receiving the care most appropriate for their disease.

We explored in an earlier paper (Towse et al. 2022) the challenges of value attribution to conventional HTA approaches. Current payer and HTA-body approaches either assume the price of the backbone therapy is unchanged or require some arbitrary reduction in the price of products being used in combination. In the situation of an unchanged price, we considered the typical situation where the combination leads to an increase in treatment duration for the backbone therapy used as part of the combination. In this case it is only possible for any add-on therapy to be cost-effective, even at zero price, in very restricted assumptions. In such circumstances it is very unlikely that the add-on therapy will be cost-effective at a price that reflects its contribution to the value of the combination.

This paper seeks to contribute to the emerging debate on this policy challenge by articulating an approach to solving the value attribution problem. The solution we propose assumes the price of the backbone therapy will differ in combination use, as do the two alternative proposals from the literature that we compare our approach with.

We also set out in our earlier paper (Towse et al. 2022) criteria that a value attribution solution should meet. The solution should be: Universal, with the solution allowing for value attribution for most possible combination therapy configurations; Logical and symmetrical with the solution being neutral to each combination constituent, regardless of which is the backbone or the add-on; and Complete, by which we mean that the solution will always produce an attribution of the full value of the combination between the component parts.

We reiterate our view that the order of backbone and add-on sequence should not, in principle, impact the value attribution between the combination constituents. No product is “first” in the combination. The combination is only created at the point where all 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) when the clinical regimen (A+B) is identical to (B+A) in terms of the value it delivers. However, the proposal we put forward uses weights which could be adjusted to give some preference to a “first” product if that was the preference of the payer or of companies negotiating a combination price attribution.

The paper is structured as follows. We set out our assumptions and then our proposed solution. We then compare this approach with two others proposed in the literature. Finally, we discuss issues in applying our approach, notably how the challenge of partial information could be overcome, other implementation issues, and whether some of our assumptions could be relaxed.

2 Assumptions

We use the following assumptions to support the conceptual framework development:

- We assume medicine A (add-on) to be added to medicine B (backbone) to form the combination regimen. Our reference standard of care (SOC) is treatment prior to introduction of either monotherapy. We term the incremental health gain over SOC of their use in monotherapy as H_B and H_A respectively, and the incremental health gain over SOC from their use in combination as H_{B+A}. Note that we are not looking at the incremental gain as between B and A or as between either of them and the combination B+A. All of the health gain is as compared to SOC. This is because we are looking at value attribution. The total value, and therefore price(s), of a combination therapy remains anchored in incremental analysis in line with normal HTA principles. It is important to understand this distinction between establishing the total value of a combination and establishing the attribution of that value as between the products that make up the combination.

- We assume no other health system costs associated with delivering the monotherapies or combination therapies. In practice there would be other costs, and these would be taken into account using normal HTA principles. We are looking at attribution of value established after other costs have been taken into account.

- If add-on therapy A lacks evidence of its value as monotherapy, we have only partial information about H_A. We return to this later.

- To make the application of the method tractable, a cost-per-QALY paradigm with a Cost-Effectiveness Threshold (CET) set at *k* is used as an example in which we assume a treatment's value is a linear function of the incremental QALYs. We discuss later how our framework can be applied to non-QALY-based "added therapeutic benefit" systems.

- We assume the monotherapies are priced up to their threshold values, i.e. the maximum the payer is willing to reimburse. This allows us to equate the medicine's price with the incremental value to the payer.

We use the concept introduced in the earlier paper (Towse et al. 2022) of Sub-, Constant-, or Super-Additive Scale of the health gain from the combination. We use the terms Sub-, Constant-, or Super-Additive Scale of the combination to distinguish how much additional health value is generated over SOC.

Let backbone B generate more additional units of health over SOC than the add-on A, if given as monotherapy, i.e. $H_B > H_A$ thus B is preferred as a monotherapy. For illustration, let us assume that H_B = 1 QALY and H_A = 0.5 QALYs. This gives three possible additive scale scenarios:

(i) Sub-additive Scale (SubAS), where $H_B+H_A > H_{B+A}$. B+A given as combination therapy, adds (say) 1.2 QALYs i.e., H_B [=1]+ H_A [=0.5] > H_{B+A} [=1.2].

(ii) Constant Additive Scale (CAS), where $H_B+H_A = H_{B+A}$. B+A given as combination therapy adds 1.5 QALYs So H_B [=1]+ H_A [=0.5]= H_{B+A} [=1.5].

(iii) Super-additive Scale (SuperAS), where $H_B+H_A < H_{B+A}$. B+A given as combination therapy, adds (say) 2 QALYs, i.e., H_B [=1]+ H_A [=0.5] < H_{B+A} [=2].

Illustrated in Figure 1, the orange and light green bars show H_B = 1 and H_B = 0.5 respectively. Red bars show the three possible additive scale scenarios with (i) H_{B+A} = 1.2 (sub additivity); (ii) H_{B+A} = 1.5 (constant additivity); and (iii) H_{B+A} = 2 (super-additivity).

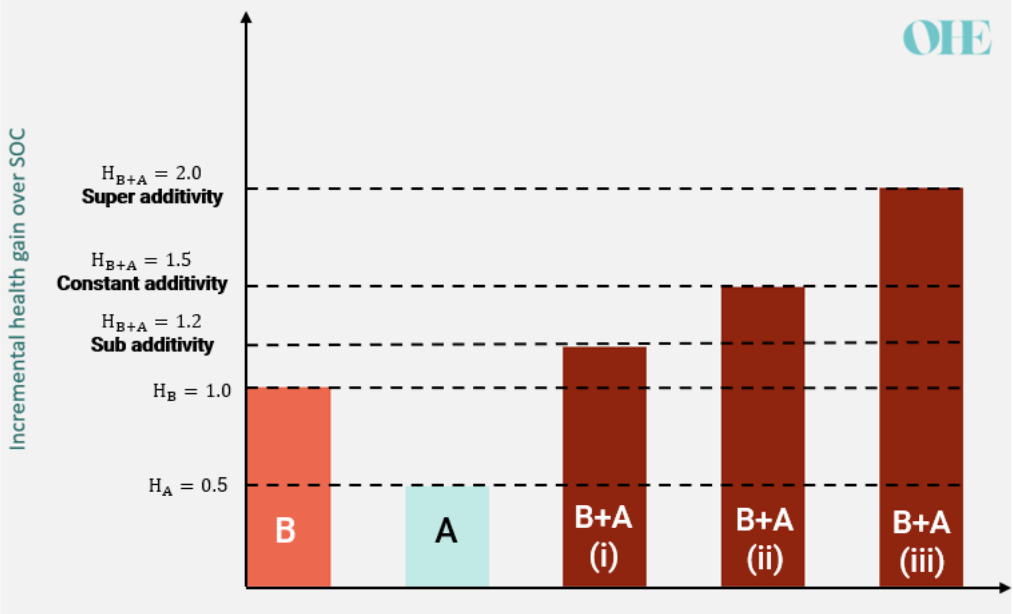

FIGURE 1: ILLUSTRATION OF CONSTANT / SUB- / SUPER- ADDITIVITY

Key: B=backbone treatment, A=add-on treatment, H=incremental health gain over standard of care (SOC

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3 General Outcome-based Value Attribution Approach Applicable to Full and Partial Information

We set out our proposed value attribution approach. In a full Information scenario, the incremental health gain over SOC of both the backbone in monotherapy H_B and the add-on A in monotherapy, H_A, are known, as well as the incremental health gain over SOC of the combination, H_{B+A}. We illustrate this in Figure 2 below. It shows the two possible ways in which the combination health gain H_{B+A} can be arrived at:

- By adding therapy A onto therapy B: in this case, B is the backbone and A the add-on. For ease of illustration we use the term $H_{A'}$ to indicate the additional health gain that add-on A brings to backbone B when used in combination, i.e. $H_{A'} = (H_{B+A} - H_B)$;
- By adding therapy B onto therapy A: in this case, A is the backbone and B the add-on. We use the term $H_{B'}$ to indicate the additional health gain that add-on B brings to backbone A when used in combination, i.e. $H_{B'} = (H_{B+A} - H_B)$.

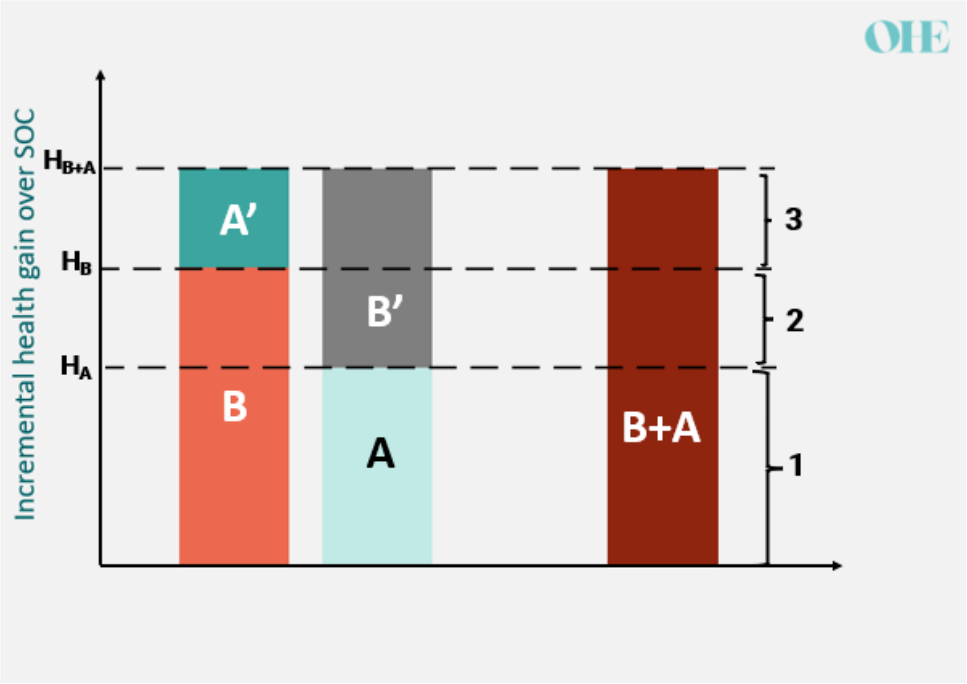

FIGURE 2: GENERAL VALUE ATTRIBUTION FRAMEWORK WITH FULL INFORMATION

The approach we propose to attribute the overall value of the combination therapy (where the combination therapy refers to a treatment-regimen in which the backbone and the add-on are given

simultaneously and the comparator is the SOC prior to the use of any of the on-patent monotherapies used in the combination) uses the intuitive concept illustrated in Figure 2.

We use $V_a(B)$ and $V_a(A)$ as the value attribution shares of the total value of the combination V(B+A) (over and above the SOC as defined above). $V_a(B)$ and $V_a(A)$ both range between 0 and 1 and $V_a(B) + V_a(A) = 1$. For illustration we are using the cost-per-QALY framework, which assumes value to be a linear function of health gain. We can therefor assume $V(B+A)=k\ H_{B+A}$. Table 1 below disentangles how the value is attributed in this proposed general approach.

TABLE 1: GENERAL VALUE ATTRIBUTION FRAMEWORK BREAKDOWN

	Backbone (B)	Add-on (A)
Monotherapy effect	H_B / H_{B+A}	H_A / H_{B+A}
Additional effect	$(H_{B+A} - H_A)$ / H_{B+A}	$((H_{B+A} - H_B)$ / H_{B+A}
Value attribution shares	$V_a(B) = \{H_B + (H_{B+A} - H_A)\}$ / 2* H_{B+A}	$V_a(A) = \{H_A + (H_{B+A} - H_B)\}$ / 2* H_{B+A}

The value attribution for each combination product is derived as the arithmetic average of the monotherapy and add-on effect for each of the products (with an equal weight of 0.5 given to the monotherapy and add-on effect for each of B and A in their respective value attribution derivation). We illustrate with two simple numerical examples.

Simple Numerical Examples of two products in combination

Example 1: With an example whereby (say) $H_B = 7$ QALYs, $H_A = 3$ QALYs, and $H_{B+A} = 9$ QALYs, then as $V(B+A) = k^* H_{B+A}$, so:

$V_a(B) = \{H_B + (H_{B+A} - H_A)\} / 2^* H_{B+A} = (7+ 9 - 3) / 18 = 0.722$

$V_a(A) = \{H_A + (H_{B+A} - H_B)\} / 2^* H_{B+A} = (3 + 9 - 7) / 18 = 0.278$

In other words, product B gets over 70% of the combined value of 9 QALYs (0.722*9 = 6.5 QALYs) and product A gets around 30% of the value (0.278*9 = 2.5 QALYs).

Example 2: With an example whereby (say) $H_B = 7$ QALYs, $H_A = 5$ QALYs, and $H_{B+A} = 9$ QALYs, then as $V(B+A) = k^* H_{B+A}$, so:

$V_a(B) = \{H_B + (H_{B+A} - HA)\} / 2^* H_{B+A} = (7+9-5) / 18 = 0.611$

$V_a(A) = \{H_A + (H_{B+A} - H_B)\} / 2^* H_{B+A} = (5+9-7) / 18 = 0.389$

In other words, product B gets around 60% of the combined value of 9 QALYs (0.611*9 = 5.5 QALYs) and product A gets around 40% of the value (0.389*9 = 3.5 QALYs).

An Alternative Equivalent Illustration

We can look at an alternative equivalent way to illustrate and derive the proposed value attribution. The importance of this way of approaching attribution is that it is a more generalisable approach in two important respects:

- It can be used for more than two products.
- By breaking down the component parts, different assumptions about the weighting of attribution shares (as between the products comprising the combination) can be made for each segment of the value of the combination;

The total combination value for two products can be separated into three key outcomes segments as identified by the arrows in Figure 2. Note that:

- Segment 1 is a joint outcomes segment for the two monotherapies. Up to this minimum point of H_A both B and A are equally effective. Arguably the split of value share (the weights given to the shares of B and A of this segment) should be 50-50%.
- Segment 2, between the minimum point of H_A to the maximum point of H_B, is a superior treatment segment for one of the two monotherapies (B). Arguably, the better treatment (B) should get a weight (share) of 100% of this value.
- Segment 3 is the incremental outcomes segment from the combination, above H(B). Arguably B and A share this incremental B+A combination outcome equally, i.e. with 50-50% weights for this segment of the value.

The value attribution for each product making up the combination is given by the weighted average of its value attribution weights over each of the three outcome segments. We set this out in Table 2 below.

This value attribution approach may seem more complicated, but it has two major advantages. Firstly, it can easily be extended to handle any number of constituent therapies in a given combination therapy. Secondly, it can be used to apply different weights (shares) of each segment of outcome (value) as between the products (B and A in our two-product combination). We return to this point later.

TABLE 2: GENERALISED VALUE ATTRIBUTION FRAMEWORK BREAKDOWN

Outcome Segment	Outcome Segment, proportion (α_i) of the total	Treatment value attribution weights to the component products	
		$V_{aw,i}(A)$	$V_{aw,i}(B)$
1.	$\alpha_1 = H_A / H_{B+A}$	1/2	1/2
2.	$\alpha_2 = (H_B - H_A)/ H_{B+A}$	0	1
3.	$\alpha_3 = (H_{B+A}) - H_B)/ H_{B+A}$	1/2	1/2

Based on the division of the combination into outcomes segments and the value attribution weights given to each product by segment, the value attribution for (say) product X ($V_a(X)$) is defined as the weighted average across the outcomes segments: $V_a(X) = \sum \alpha_i * V_{aw,i}(X)$.

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We assume for illustrative purposes that k =1 so V and H take the same value. In our Example 2 above we had H_B = 7 QALYs, H_A = 5 QALYs, and H_{B+A} = 9 QALYs. It then follows that:

- Segment 1 has 5 QALYs out of the total of 9 (a proportion of 0.556) with weights as between the two products of 50:50 (2.5 QALYs each). Each gets an attribution share from this segment of 0.556 x 0.5 = 0.278
- Segment 2 has 2 QALYs which accrue 100% to B (2 QALYs to B). This segment has a proportion of 2/9 = 0.222, with a weight of 1 going to B. So B's attribution share is 0.222 and A's is zero.
- Segment 3 has 2 QALYs divided 50:50 (1 QALY each). This segment also has a proportion of 2/9 = 0.222, but with a weight of 0.5 for each of B and A. Each gets an attribution share from this segment of 0.222 x 0.5 = 0.111

If we add up the QALYs, product B gets 5.5 QALYs and A gets 3.5 QALYs which are attribution shares of 0.611 and 0.389. If we apply our summation $V_a(X) = \sum \alpha_i * V_{aw,i}(X)$ formula then B gets a value attribution of (0.278+0.222+0.111) = 0.611 and A gets (0.278 + 0 + 0.111) = 0.389.

Note that we only have equivalent outcomes between the first and the second approach because we are assuming equal weights (50:50) for value attribution in Segments 1 and 3.

An Illustration of Outcome Attribution for a Triplet Combination

The proposed approach can be easily extended to handle combinations with more than two therapies. Below follows a description of how to handle value attribution for triplets (Figure 3 and Table 3). An extension of the approach for quadruplets is provided in Appendix 1.

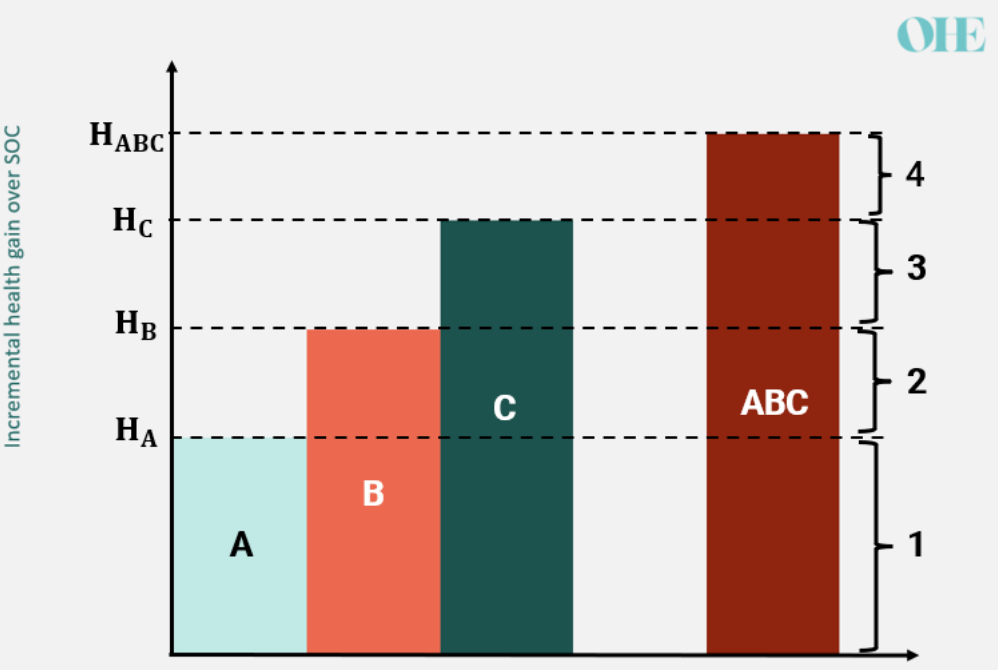

FIGURE 3: FULL INFORMATION VALUE ATTRIBUTION – TRIPLETS

TABLE 3: TRIPLET TREATMENT VALUE ATTRIBUTION BY OUTCOMES SEGMENT

Outcome Segment	Outcome Segment, proportion (α_i) of the total	Treatment value attribution weights to the component products		
		$V_{aw,i}(A)$	$V_{aw,i}(B)$	$V_{aw,i}(C)$
1.	$\alpha_1 = H_A / H_{A+B+C}$	1/3	1/3	1/3
2.	$\alpha_2 = (H_B - H_A) / H_{A+B+C}$	0	1/2	1/2
3.	$\alpha_3 = (H_C - H_B) / H_{A+B+C}$	0	0	1
4.	$\alpha_4 = (H_{A+B+C} - H_C) / H_{A+B+C}$	1/3	1/3	1/3

As for the duplet combination, the value attribution for product X ($V_a(X)$) is defined as the weighted average value attribution across the outcomes segments: $V_a(X) = \sum \alpha_i * V_{aw,i}(X)$

We assume equal weights across all treatments making up the combination in outcomes segment I (when they are equally effective) and in segment II as between treatment B and C, and in the combination outcomes segment IV (when all treatments share the increment outcomes of the combination above the best of the individual treatment equally). The proposed equal weights for value attribution for these segments is a logical starting point in ensuring a logical and symmetric framework for value attribution. The suggested outcomes segment weight can, however, be revised and modified to capture a range of other scenarios and outcomes. For example, if a view was taken to give some priority to the current monotherapy used (B) then segment I could give a higher weight than 0.5 to product B. With this flexibility, the proposed approach is offering a general value attribution framework.

4 Comparison with Other Proposed Approaches

We have previously (Towse et al, 2022) outlined two approaches in the literature and analysed their impact when used for value attribution.

- A "partial information incremental outcomes value attribution approach". The backbone therapy now attains its value and cost from its monotherapy use (with cost capped at the monotherapy cost level) and the add-on therapy is attributed the value of the incremental combination outcomes. This means that the value of the add-on is based on the health gain ($H_{B+A} - H_B$). The proposed value attribution for the add-on therapy A is therefore given by the incremental combination outcome proportion relative to the overall combination outcomes, i.e., $V_a(A) = (H_{B+A} - H_B) / H_{B+A}$. The value attribution for the backbone therapy is correspondingly given by the proportion of the backbone monotherapy outcome relative to the combination outcome, i.e., $V_a(B) = H_B / H_{B+A}$. The backbone retains its absolute value, and the add-on gets what is left – in effect a "residual" approach. Two pragmatic arguments are put forward for this approach. Firstly, it is argued that if we lack information on the monotherapy value of A, then this is the obvious approach to take. Secondly, if we are in a company bargaining environment then any solution that gives the owner of product B less value (and therefore revenue) than it currently gets is unlikely to be successful.

- A "full information monotherapy ratio approach" with data available for each component. This approach recognises the importance of both products in contributing to the value of the combination therapy by using a simple ratio of the sum of their respective monotherapy values. Thus the attribution shares of the backbone and add-on therapy are, respectively, $V_a(B) = H_B / (H_A + H_B)$, and $V_a(A) = H_A / (H_A + H_B)$.

We compare the results from applying these two approaches versus the results of the general (outcome-based) value attribution approach with full information that we propose, using two case studies, and for each of the three scenarios of SubAS, SuperAS and CAS, in Appendix 2.

In summary, we find that:

- Given that SubAS is, in our view, likely to be the norm, i.e. that $H_B + H_A > H_{B+A}$, i.e. the total value of the combination therapy is less than the sum of the values of each constituent in the combination as monotherapy, then the incremental value approach will undervalue the add-on therapy, as compared to both the monotherapy approach and our general approach, with important consequences for the incentive to innovate. This is because it ignores the likely value of A as a monotherapy, and as a consequence assumes product B is as effective (in terms of generating health gain) in combination as it is in monotherapy.

- Using the monotherapy ratio approach in the (usual) case of SubAS overvalues the add-on therapy and undervalues the backbone therapy. This is because the add-on is contributing less to the combination than its monotherapy value. In effect we have the opposite problem to that of the incremental approach. Instead of overvaluing B, we are now overvaluing A. We note, of course, that this approach would undervalue the add-on therapy in the case of SuperAS, however, it is not a case of "swings and roundabouts", we need a credible approach for SubAS situations. In the extreme, if the monotherapy value of the add-on is close to 0, then a monotherapy ratio approach would give all of the value of the combination to the backbone therapy.

- Our approach gives results in between the other two approaches. This is because it seeks to draw on each of these. It incorporates the contribution of the add-on (A) to the backbone (B), but it also incorporates the alternative in which B is the add-on therapy to A. In this way it is taking account of the relative monotherapy values of A and B. Hence its value will lie between the other two in the case of SubAS and SuperAS.

- All three approaches give the same results as each other if we have CAS, with a resulting value attribution of 0.5 to each component of the combination. However, there is no reason why most combinations are likely to have CAS.

In Towse et al. (2022) we compared the attributable share of the two approaches against the degree of additivity for Example 1. We reproduce this Figure, adding in the shares attributable using the full information general outcomes approach we are proposing. The results are set out in Figure 3 below.

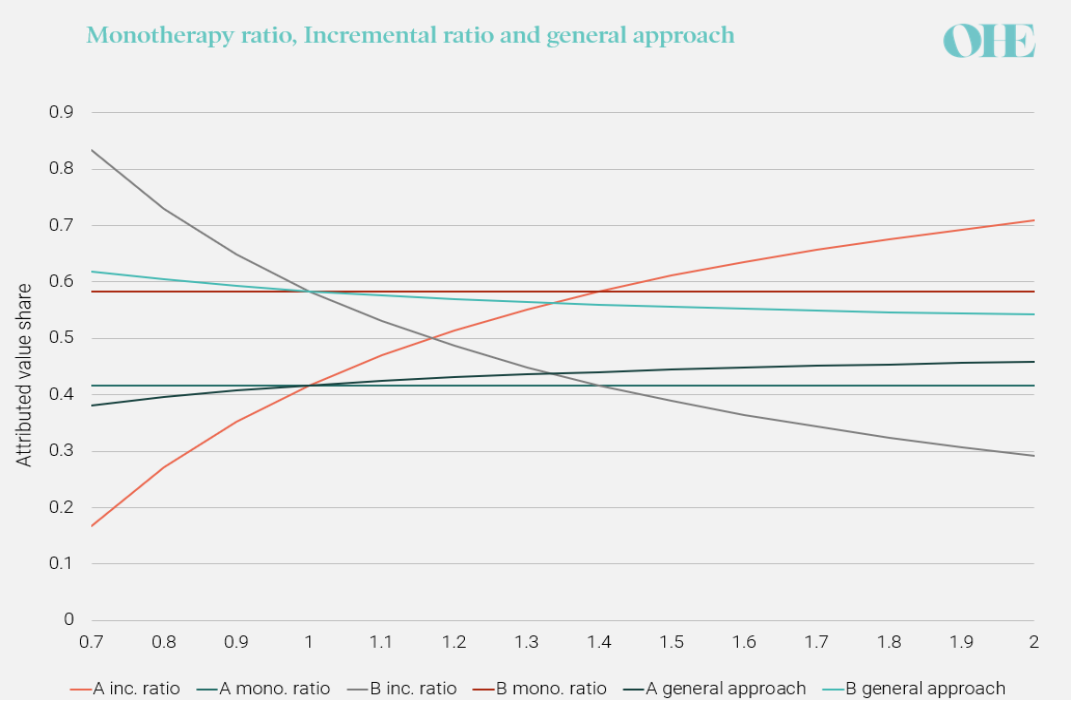

FIGURE 4: COMPARISON OF THE THREE APPROACHES IN RELATION TO THE DEGREE OF ADDITIVITY

We can see very clearly that the general approach we are proposing lies in between the two alternative approaches. This reflects the fact that it combines elements of each of them. We can see that as the degree of additivity moves further away from 1 in either direction, then our general approach ratios also move, reflecting the impact of the incremental value.

To provide further insight into the comparison of the value attribution approaches Table 4 below describes the properties of each approach in the SubAS, CAS and SuperAS domains for each value attribution approach to further understand the general patterns and relationships between the approaches. The degree of additivity is given by λ. In the limits of the scenario of increasing additive scale, the combination outcomes will be much bigger than individual components. These scenarios may therefore not represent entirely plausible outcomes but are shown to gain insight into key properties of how the different value attribution approaches perform over a wide range of additive scale situations.

TABLE 4: VALUE ATTRIBUTION PROPERTIES AND CONVERGENCE ACROSS ADDITIVITY SCENARIOS

Degree of Additivity λ	Mono ratio		Incremental approach		General approach	
	$V_a(B)$	$V_a(A)$	$V_a(B)$	$V_a(A)$	$V_a(B)$	$V_a(A)$
SubAS, $0 < \lambda < 1$, H_{B+A} ➔ $\max(H_A,H_B)$ $H_B>H_A$, λ ➔ $H_B/(H_B+H_A)$	$H_B/(H_B+H_A)$	$H_A/(H_B+H_A)$	➔ 1	➔ 0	➔ $1-H_A/2*H_B$	➔ $H_A/2*H_B$
CAS, $\lambda = 1$	$H_B/(H_B+H_A)$	$H_A/(H_B+H_A)$	$H_B/(H_B+H_A)$	$H_A/(H_B+H_A)$	$H_B/(H_B+H_A)$	$H_A/(H_B+H_A)$
SuperAS, $\lambda > 1$ When $\lambda \rightarrow \infty$	$H_B/(H_B+H_A)$	$H_A/(H_B+H_A)$	➔ 0	➔ 1	➔ 1/2	➔ 1/2

n.b. λ = degree of additivity, i.e. $\lambda = H_{B+A} / (H_A + H_B)$

As seen from Table 4:

- The monotherapy ratio approach consistently provides a constant ratio across all additive scale scenarios, which indicates the lack of including the actual combination outcomes (whether they are SubAS, CAS, or SuperAS) as an input to the value attribution;

- With SubAS, at the limit as H_{B+A} ➔ $\max(H_A,H_B)$, as we are assuming that the backbone B provides the largest monotherapy outcome (towards which the combination outcome is converging), the incremental approach converges with λ ➔ $H_B/(H_B+H_A)$ as stated in LHS Table column for the SubAS case. This provides all value to the backbone and zero value attribution to the add-on, regardless of the difference between the add-on and the backbone as monotherapies. In this scenario the general value attribution approach, in contrast, converges towards attributing $H_A/2*H_B$ to the add-on and $1-H_A/2*H_B$ to the backbone, consistent with the illustration outlined above whereby backbone would get only half of the share of the first outcomes segment H_A/H_B where the backbone and add-on are equally effective.

- With CAS, then the monotherapy ratio approach produces the same results as the incremental approach and our general approach, so we can show this at its simplest as $V_a(B) = H_B/(H_B+H_A)$ and $V_a(A) = H_A/(H_B+H_A)$. We can see the convergence of the different approaches towards the same value attribution outcomes for the CAS case ($\lambda = 1$) in Figure 4.

- With increasing SuperAS the general approach tends to a 50:50 distribution, while the incremental value approach gradually provides less and less to the backbone with gradually increasing value attribution to the add-on. This value attribution is independent of the actual outcome provided by the monotherapy add-on. In the limit with increasing degrees of additivity this seems to lead to a very fundamental skewed value attribution assignment with the backbone getting zero. As the outcome of the combination would not be possible without the inclusion of the backbone, not attributing any value to the backbone seems an extreme and implausible solution to the value attribution problem. The general approach, on the other hand, converges to an equal split for each component with increased additive scale λ.

5 The Partial Information Scenario

In partial information scenarios, where outcomes data are missing for one or more monotherapies, the proposed full information general outcome-based approach outlined above still allows value attribution to be derived for each component of the combination by using the estimated monotherapy outcomes data as input to the value attribution.

Approach to Address Partial Information

In the previous sections we have established an alternative general H_{A+B+C} for combination products that also holds under SubAS. However, the usefulness of that approach hinges on knowing or being able to estimate the health gains from the missing monotherapy outcomes data (i.e. of treatment A as a monotherapy in the example above). We propose to use a Bayesian approach to estimate the expected outcomes of the constituent part for which there is no data, by defining a prior distribution of its efficacy as monotherapy on the outcome of choice in the value attribution framework.

As the outcome of the value attribution framework under partial information is sensitive to the type of prior distribution, methods for defining it in a robust way are important. Generally, the prior distribution should be informed by the logical constraints of the parameter and the form of the data. Rules of thumb exist to aid the selection of distributions for specific parameters, like probability of disease progression or time-to-event estimates (Briggs, 2006). For example, when constructing a prior distribution of the expected health gain from treatment A as a monotherapy, the normal distribution would be a candidate due to the central limit theorem, which is based on asymptotics, also accounting for limitations of possible range of outcomes considering restrictions imposed under various additive scale scenarios (under SubAS, the implied range of the add-on is that $H_A > H_{B+A} - H_B$). However, in the context of value attribution under partial information, this prior distribution of the efficacy of treatment A as a monotherapy, like many other prior distributions, needs to be constructed with no or very little data. In such situations, when the value of the quantity of interest is critical to policy decisions and ordinary statistical approaches cannot provide a (timely) answer, the prior distribution needs to be *elicited*, using a structured expert elicitation (SEE) approach.

To define the shape of a distribution using SEE, a number of summaries need to be elicited for each quantity. Published applications of SEE have typically used one of two approaches: fixed interval method (FIM) or variable interval method (VIM). In an FIM, experts are provided with ranges of values and asked to assess the probability that the quantity lies in each. In a VIM, experts are asked to specify values of the quantity of interest for predefined percentiles of the distribution. Applications using VIM elicit either quartiles of the distribution or credible intervals, and in general ask for a very limited number of summaries. Studies using FIM often choose the "chips and bins" method (histogram technique or probability grid). This method defines a larger number of intervals (typically up to 20) and asks the expert to distribute a fixed number of chips across these intervals. The more chips placed in a particular interval, the stronger the belief that the true value of the quantity of interest lies in that interval (Soares et al., 2018).

As a next step, a value of information (VOI) approach is proposed to address the question as to whether additional evidence should be generated to improve the estimates of value in monotherapy. In essence, applying a VOI approach to this decision problem under partial information would estimate the probability of making an incorrect value attribution in the absence of data on H_A and quantify the costs associated with that (Fenwick et al., 2020). In this context, the 'costs' would first and foremost be the costs in terms of uncaptured revenue to the manufacturer of not being able to

sell the drug at the price that reflects the 'true' value attribution. This provides an upper bound to the 'value' of collecting information to (better) estimate H_A, e.g. in a trial. The question as to when a trial for the add-on drug in monotherapy may or may not be worthwhile for the manufacturer to undertake could thus be informed. If the costs of performing a study on treatment A as monotherapy would be lower than the cost of not getting the 'right' value attribution, this may argue for doing such a trial (if ethically and practically feasible). If the cost of doing such a study would outweigh the expected revenue gain from justifying a price that reflects the true value attribution, this may not be worth it.

We consider this to be a valid and important approach to the use of partial information. It is work in progress and more thought will need to be given to the types of evidence that may be available on one, or both, of the drugs, and how this can be most efficiently used to estimate attribution values.

We also note that there are other relevant costs that may arise, for example if the incorrect attribution leads the manufacturer not to launch the product, thus depriving patients of access to the health gain the product would provide. These broader issues raise the question as to whether the payer (or its HTA body) should become involved in value attribution as well as in assessing the value-for-money of, or price relevant to, the combination.

6 Generalising the Value Attribution Framework

For ease of development and explanation we have used the example of a simple cost-per-QALY based HTA system, and two products. However, the framework we have set out is generalisable in the following ways:

- The outcomes do not have to be QALYs translated into value by a factor *k*. The vertical axes in Figures 1-3 can reflect any outcome measure (or composite 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 other words, providing we have the same outcome measure for the combination and for all parts of the combination as monotherapies the value attribution approach we have set out can be applied.

- As we show, more than two products can be combined and have the total combination value attributed as between them, providing we have available outcomes or are able to make plausible estimates of the monotherapy outcomes for each component.

- We also set out assumptions as to how value should be divided within different outcomes segments. For example, we assumed 50-50% weights for the attribution of value as between the combination components for the outcomes segment of the incremental gains above the best of the monotherapies. These can be modified within this proposed overall approach. If, for example, one wished to give more weight to the backbone (B) than the add-on (A) then one option would be to give more of the first and / or third segment of value in Table 2 (α_1 or α_3) to B than the 50% we assumed. We have argued very strongly for neutrality as to who comes first, but the mechanism allows other assumptions to be made and we are very aware of arguments that could support greater weighting for the incumbent backbone.

7 Implementation Issues

We recognise that value attribution cannot be implemented without some form of price adjustment mechanism for the backbone (and the add-on if it already has a monotherapy use price). However various approaches to price-adjustment depending on the use of the drug are being considered and, in some cases, have been implemented to make this happen (Neri et al., 2018, Cole et al., 2021).

We also recognise that a number of payers and HTA bodies see it as the responsibility of the companies to come forward with an agreed attribution proposition, i.e. the only interest of the health system is the combined price being offered. However, we are sceptical that efficient solutions will be found compatible with competition law, enabling companies to negotiate on a product by product, market by market basis. Without an agreed value attribution mechanism this is likely to be very resource intensive. We are of the view that it is inevitable that payers and HTA bodies will be drawn into value attribution, and the sooner this begins the better.

We recognise that any proposed solution to the lack of information about the efficacy of the add-on in a monotherapy setting may be contestable, particularly if it relies on SEE. However, reference case methods for SEE have been developed that allow the use of different methods, depending on the decision-making setting (Bojke et al., 2022).

8 Next Steps

We have set out a generalised value attribution framework which can be used to attribute value (and therefore prices) as between the component parts of a combination therapy. 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, such that companies have a basis for negotiation. 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.

We also recognise that handling the (most common) scenario of partial information will be key to progressing this framework and further research is needed in this area.

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Appendix 1: Extension of Value Attribution Framework to Quadruplets

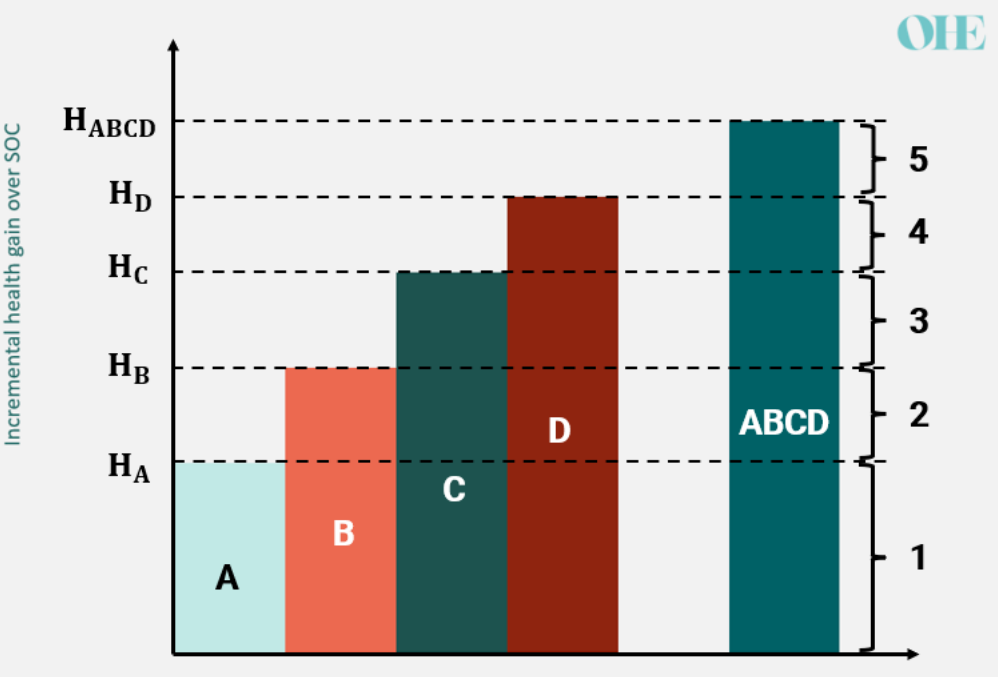

FIGURE A1: FULL INFORMATION VALUE ATTRIBUTION – QUADRUPLET

TABLE A1: QUADRUPLETTREATMENT VALUE ATTRIBUTION BY SEGMENT

Segment		Treatment value attribution weight distribution by segment			
No.	Outcome segment proportion * (α_i)	$V_{aw,i}(A)$	$V_{aw,i}(B)$	$V_{aw,i}(C)$	$V_{aw,i}(D)$
1.	$\alpha_I = H_A / H_{A+B+C+D}$	1/4	1/4	1/4	1/4
2.	$\alpha_{II} = (H_B - H_A) / H_{A+B+C+D}$	0	1/3	1/3	1/3
3.	$\alpha_{III} = (H_C - H_B) / H_{A+B+C+D}$	0	0	1/2	1/2
4.	$\alpha_{IV} = (H_D - H_C) / H_{A+B+C+D}$	0	0	0	1
6.	$\alpha_V = (H_{A+B+C+D}) - H_D) / H_{A+B+C+D}$	1/4	1/4	1/4	1/4

Value attribution for product X is $V_a(X)$ and is as before defined as the weighted average value attribution across the outcomes segments: $V_a(X) = \sum_i * V_{aw,i}(X)$

Appendix 2 Comparing the Three Value Attribution Approaches

Here we set out how the attribution of value in a General Full Information Outcomes Value Attribution Framework differs from two other approaches - Partial Information Incremental Outcomes Approach and the Full Information Monotherapy Ratio Approaches with two Examples using each of SubAS, SuperAS and CAS.

In the following, let $V_a(B)$ and $V_a(A)$ denote the value attribution *shares* of the value of the combination, i.e., $V_a(B) + V_a(A) = 1$. To recap, the attribution shares are calculated in the following ways:

- General Full Information Value Attribution Framework. Here we have $V_a(B)= \{H_B + (H_{B+A} - H_A)\} / 2* H_{B+A}$, and $V_a(A) = \{H_A + (H_{B+A} - H_B)\} / 2* H_{B+A}$.
- Incremental (Partial Information). Here the add-on therapy is attributed the full incremental health gains of the combination versus the backbone monotherapy given. This is $H_{B+A} – H_B$. In this case the attributions are $V_a(B)= H_B / H_{B+A}$ and $V_a(A)= (H_{B+A} – H_B) / H_{B+A}$.
- Monotherapy Ratio (Full Information). The value attribution for each component is simply the ratio of the monotherapy outcomes to the sum of their respective monotherapy values. The value attribution for backbone is therefore $V_a(B)= H_B / H_{B+A}$, and for add-on $V_a(A)= H_A / H_{B+A}$

We set out in Table A3 the value attribution shares for each of the three approaches in two Examples for the SubAS, SuperAS and CAS scenarios.

TABLE A3: ADDITIVITY EXAMPLES WITH ALTERNATIVE ATTRIBUTION APPROACHES

	QALY gain	General approach	Incr. ratio	Mono ratio	QALY gain	General approach	Incr. ratio	Mono ratio
	Example1				*Example2*			
SubAS	= 0.9				=0.75			
Backbone H_B	7	0.722	0.778	0.700	7	0.611	0.778	0.583
Add-on H_A	3	0.278	0.222	0.300	5	0.389	0.222	0.417
Combo H_{B+A}	9				9			
Sum of mono H_B+H_A	10				12			
CAS	=1				=1			

Backbone HB	7	0.700	0.700	0.700	7	0.583	0.583	0.583
Add-on HA	3	0.300	0.300	0.300	5	0.417	0.417	0.417
Combo HB+A	10				12			
Sum of mono HB+HA	10				12			
SuperAS	=1.5				=1.25			
Backbone H_B	7	0.633	0.467	0.700	7	0.567	0.467	0.583
Add-on H_A	3	0.367	0.533	0.300	5	0.433	0.533	0.417
Combo H_{B+A}	15				15			
Sum of mono H_B+H_A	10				12			

We have two Examples. In both H_B =7. In Example 1 the sum of the monotherapies $H_B + H_A$ is 10 and in Example 2 it is 12. We then have three scenarios:

1. SubAS in which the combined therapy delivers 9 QALYs, i.e. H(B+A) = 9.

2. SuperAS in which the combined therapy delivers 15 QALYs, i.e. H(B+A) = 15

3. CAS the combined therapy delivers 12 QALYs, i.e. H(B+A) = 12

Table A3 shows a comparison of the three approaches for our SubAS Example 2 illustrated in the main paper with backbone H_B = 7, and add-on H_A = 5, and the combined health gain H_{B+A} = 9. The sum of the monotherapy health gains H_B+H_A = 12. In Example 1 we have the same values for backbone H_B = 7 and the combined health gain H_{B+A} = 9, but with add-on H_A = 3. In Example 1, the sum of the monotherapy health gains H_B+H_A = 10.

We have two Examples of SubAS, and it can be seen that:

- In both Examples, the General Approach gives an attribution share that is in between the other two approaches;

- in Example 2 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) as compared with the partial information incremental value attribution approach which, gives a value share of 0.222 to the add-on and 0.778 to the backbone.

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- In Example 1 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 Example 2 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 in this Example because the degree of sub-additivity is less in Example 1, i.e. the benefits of the sum of the two monotherapies is closer to the value of the combination (10 versus 9) as compared to Example 2 (12 versus 9).

- 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 as each other and as the General Approach. We discuss a CAS example later.

The overall effect is, however, clear in both Example 1 and Example 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. The General Approach addresses this problem by weighting both the relative contributions of the products as monotherapies and what they add as an incremental therapy to a combination using the other product as the starting point.

We can see that in the scenario of SuperAS:

- In both Examples, the General Approach gives an attribution share that is in between the other two approaches;

- In the SuperAS cases 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. The partial information incremental value attribution approach depends on the absolute health gain, which is higher in the SuperAS situtation, with H_{B+A} = 15 QALYs as compared to 9 QALYs in the SubAS situation.

- Again the monotherapy ratio value attribution shares are the same in Examples 1 and 2 and the same as in the SubAS situation, because these shares do not depend at all on the absolute health gain achieved by the combination regimen.

- The overall effect is, however, clear in both Example 1 and Example 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 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.

- The General Approach gives a value attribution in between the two approaches because it weights both the relative contributions of the products as monotherapies and what they add as an incremental therapy to a combination using the other product as the starting point.

In our view 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.

We can see that in the scenario of CAS:

- All three approaches give the same result;
- The only situation where the sequence order does not matter for the incremental approach is if constant additive scale (CAS) holds. Otherwise it gives a different value attribution depending on which product is used as monotherapy. 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.

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