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AN INDUSTRY PERSPECTIVE OF VALUE ATTRIBUTION FRAMEWORKS

Unlocking the Value of Combination Therapies

CONTRACT RESEARCH REPORT
JULY 2024

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Executive Summary

Combination therapies (CTs) merge treatments with different mechanisms of action to achieve greater clinical benefits than the individual components alone. CTs are increasingly being used in oncology. However, when these therapies involve two or more on-patent drugs from different manufacturers, assessing and pricing them can be challenging, potentially delaying or preventing patient access. One significant issue is fairly apportioning the value of a CT among its components based on their contribution to the overall effectiveness. The balance of market power among the manufacturers can also influence value attribution.

The current approach to value attribution is the incremental value (IV) method. However, this method faces challenges in assessing cost-effectiveness and may not fairly attribute value except in cases of constant scale of additivity. Recent alternatives, such as the monotherapy ratio (MR) and generalized approach (GA), have been proposed to address these issues.

The Office of Health Economics (OHE) developed an Excel tool to compare the value attribution shares under each value attribution framework (VAF). This tool was piloted by the Association of the British Pharmaceutical Industry's (ABPI's) combination treatment project team, a group of ABPI member companies that have a specific focus on the issues and solutions surrounding access to combination therapies. Feedback was gathered from the project team through a qualitative survey. This paper presents the industry's perspective on the VAFs, highlighting their strengths and weaknesses, ease of implementation, and considerations for further engagement.

Although no single solution was deemed ideal, the GA received the most support as a preferred VAF. It was considered a sensible, risk-mitigating approach for portfolios that include both backbone and add-on therapies. Key themes in evaluating the VAFs included fairness in value attribution shares, feasibility, uncertainty of inputs and outputs, and accuracy in cases of sub- or super-additivity. IV was seen as the simplest and most feasible but insufficient for overcoming access challenges for CTs. Each VAF had weaknesses: the MR and GA frameworks require extensive information, the GA approach is complex, and the IV method fails to address certain cost-effectiveness issues.

Factors influencing industry and HTA engagement included the "not cost-effective at zero price" problem, the need for inter-company dialogue, payer and decision-maker acceptance of VAFs, and commercial strategy implications. While each approach has its strengths and weaknesses, with varying complexity and evidence requirements, the GA was generally considered the most appropriate for a range of products including backbones and add-ons. However, the MR or IV frameworks could also be considered in specific HTA and pricing negotiations.

Based on the results of this study, we recommend the GA as the starting point for thinking about value attribution in the arbitration process, especially under scenarios of sub- and super-additivity. However, the selection of the GA depends on the availability of evidence and the ability to generate relevant evidence. The discussion between manufacturers and payers could also be supplemented by the shares generated using the IV and MR approaches.

1 Background

Combination therapies (CTs) are treatments in which patients are given two or more drugs, that have distinct but complementary mechanisms of action, to treat a single condition. Add-on treatments, designed to work in combination with an existing, on-patent backbone therapy, have become more common, particularly within oncology. This rise in combination treatments presents challenges to conventional HTA methodologies, especially when treatments are made by different manufacturers.

There are four main challenges in the assessment and pricing of CTs: incentives, competition law, value attribution and implementation problems. These have previously been described elsewhere e.g. in Latimer et al., 2021and Towse et al., 2021. Whilst each challenge is important in its own right, Towse et al. (2021) consider solving the problem of value attribution as an essential prerequisite to solving the other issues, and hence this paper focuses on that.

When an add-on treatment is developed to be part of a combination with an existing backbone treatment, the price of that backbone treatment remains unchanged from its price as a monotherapy unless multi-indication pricing is used. The patented backbone therapy is likely to be priced up to the cost-effectiveness threshold and will probably stay at that price in a combination treatment. If the combination therapy extends a patient's life, the backbone therapy will need to be administered for the entire duration of that extended life. As a result, any additional cost for the add-on therapy pushes the total price beyond the cost-effectiveness threshold, making the add-on therapy not cost-effective at a zero price (NCZP), regardless of the survival benefits' duration (Latimer, Towse, and Henshall, 2021). An instance of this NCZP issue occurred during the National Institute for Health and Care Excellence (NICE) evaluation of pertuzumab combined with trastuzumab and docetaxel for breast cancer.

Even in cases where the add-on therapy can reasonably command a positive price, this price is unlikely to accurately reflect its contribution to the overall value of the combination therapy. This may create problematic incentives, where a potential add-on manufacturer is more likely to focus on developing monotherapy products instead of products to be used in combination with existing therapies. This could prevent patients from accessing combination therapies that are more effective than existing or potential monotherapies.

Therefore, different methods of value attribution are necessary, where the backbone and add-on therapies are priced differently than they would be if sold individually. Value attribution frameworks (VAFs) aim to determine the appropriate value shares for each component therapy within a combination, reflecting their respective contributions to the overall effectiveness. These shares can then be used to estimate cost-effective prices for each therapy within the combination. By calculating value shares, companies have an evidence-based starting point from which to enter negotiations.

Three main VAFs have been proposed in the literature:

- Incremental Value (IV), representing the current standard
- Monotherapy Ratio (MR), proposed by Briggs et al., 2021
- Generalized Approach (GA), proposed by Towse et al., 2022

These approaches vary in how they deal with 1) the additivity of the components (i.e. whether the combination delivers more, equal or less health benefit than the sum of its parts), 2) their evidence requirements and 3) assumptions about the relative market power of the manufacturers of the components, and in most cases will lead to different value attribution shares. These shares impact pricing and access decisions, which in turn affect the treatment options available to patients. Thus, it is essential for stakeholders in the health technology assessment (HTA) and market access

environments—such as manufacturers, payers, and HTA agencies—to understand the strengths and weaknesses of each VAF both conceptually and in practice.

The Office of Health Economics (OHE) has developed an Excel tool to compare the value attribution shares generated by each VAF. This tool was piloted by a project team of industry representatives, and feedback was gathered through a qualitative survey. In this paper, we present the industry's perspective on the proposed solutions to the value attribution problem and considerations for their implementation.

1.1 The Value Attribution Frameworks

This section offers a high-level overview of the frameworks, illustrating the different outcomes each framework produces, and expanding on a previously published example (Briggs et al., 2021). It also outlines the information required to implement each framework, describes how each framework behaves under different additivity scenarios (definitions provided in Box 1) and explains how the frameworks can account for market power, in case this may influence realistic price ranges. For more detailed, technical descriptions of the MR and GA, we refer to Briggs et al., 2021 and Towse et al., 2022.

BOX 1: DEGREE OF ADDITIVITY DEFINITIONS

Degree of additivity (DoA) is the ratio of the overall combination (C) incremental effectiveness to the sum of the backbone (B) and add-on (A) monotherapy incremental effectiveness:

- **Sub additivity (SubAS):** C < (B+A) ➔ DoA < 1
- **Constant additivity (CAS):** C = (B+A) ➔ DoA = 1
- **Super additivity (SuperAS):** C > (B+A) ➔ DoA > 1

1.1.1 Worked example: value attribution of ipilimumab + nivolumab combination treatment versus dacarbazine

This example expands on a worked example by Briggs et al., 2021 of the MR framework using the QALY estimates presented in the committee papers for NICE TA400 and TA384. In this example, dacarbazine represents the standard of care (SOC), ipilimumab the backbone therapy (B), and nivolumab the add-on therapy (A). All input data were taken from incremental QALY estimates using dacarbazine as a common comparator. We utilise this example throughout the report to compare the value shares generated under each approach. For simplicity, we assume balanced market power between manufacturers.

Table 1 presents the inputs from the ipilimumab and nivolumab CT example.

TABLE 1 WORKED EXAMPLE OF VALUE ATTRIBUTION FOR IPILIMUMAB + NIVOLUMAB CT

Therapy	Total QALYs	Incremental QALYs versus SOC
SOC: Dacarbazine	1.23	--
Backbone: Ipilimumab	2.64	1.41
Add-on: Nivolumab	4.31	3.08
Combination: Ipilimumab + Nivolumab	4.83	3.60

Figure 1 displays this worked example to show how value is attributed under each of the approaches. The example represents SubAS, as the combination incremental effectiveness (IE) (3.60) QALYs is lower than the sum of the two monotherapy IE estimates (1.41 + 3.08 QALYs).

Below is a discussion on each of these frameworks, including how the development of the new VAFs has sought to address the limitations of previous VAFs, with reference to this example.

In the IV approach, the value of the backbone therapy in the CT is tied to its value as a monotherapy (H_B), which also fixes its price in the CT at its monotherapy price. The residual value of the CT's IE compared to the backbone ($H_{B+A} - H_B$) is attributed to the add-on therapy. This gives the backbone a first-mover advantage over the add-on manufacturer.

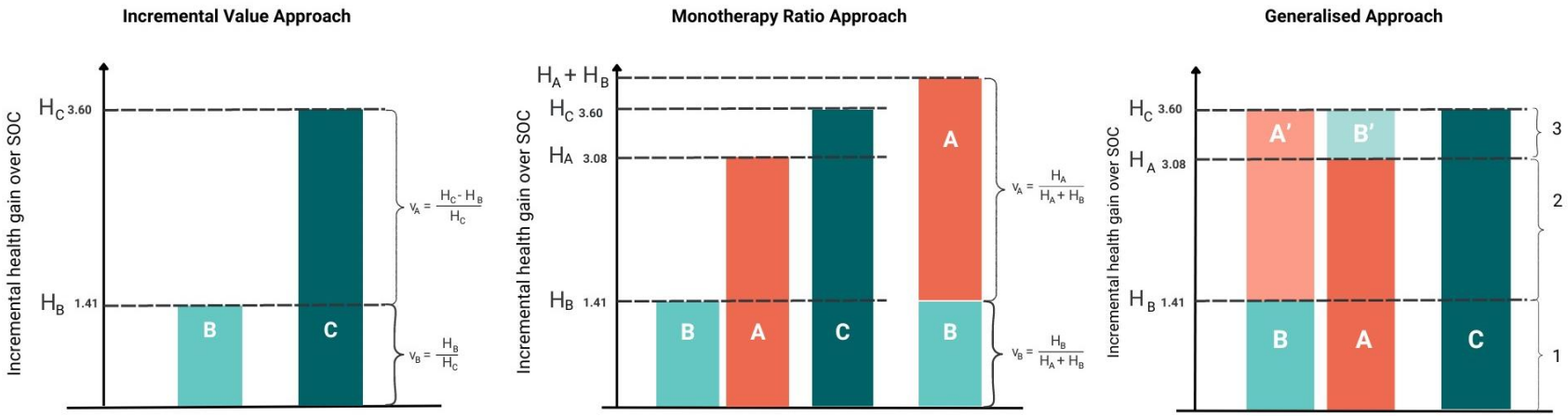
The IV approach benefits from requiring only partial information, as it uses the IE estimates of the combination and the backbone only. This makes it more practical than approaches requiring monotherapy estimates for both backbone and add-on therapies. However, by anchoring the backbone's value to its monotherapy IE, the IV approach can result in the NCZP problem for the add-on therapy (Towse et al., 2021), when the payer is not willing to pay a price that makes the combination less cost-effective than the existing monotherapy.

The MR framework (Briggs et al., 2021) addresses the NCZP issue. It is a symmetric approach (under balanced market power) that recognizes the importance of both the backbone and the add-on in contributing to the CT's value. When market power is balanced, the monotherapy incremental effectiveness estimates of B and A are used to calculate a simple ratio of each treatment to the sum of their monotherapy estimates.

For the MR approach, both monotherapy estimates are required to calculate value shares, but the CT IE estimate is only needed to determine the absolute value attributed to each therapy in the CT. Neither the IV nor MR approach considers the overall CT value in deriving shares, which leads to specific issues:

- **IV approach:** The add-on's monotherapy IE is attributed the residual value after the backbone's value is accounted for, making the IV approach asymmetric. In the worked example reflecting SubAS, the backbone is given a value share of 0.392, anchored to its monotherapy value, with the residual share of 0.608 for the add-on. This undervalues the add-on's contribution to the CT IE. The reverse is true for SuperAS.
- **MR approach:** Since it does not consider the combination's IE, the add-on is likely to be overvalued in SubAS and undervalued in SuperAS. In the worked example, the value shares for the backbone and the add-on are 0.314 and 0.686, respectively, overvaluing the backbone relative to the add-on.

FIGURE 1 APPLICATION OF VAFS TO QALY ESTIMATES FROM NICE TA400 AND TA384



B = incremental health gain of the backbone therapy compared to a common SoC, A = incremental health gain of the add-on therapy compared to a common SoC, C = incremental health gain of the combination therapy compared to a common SoC

Value share attributed to:	IV	MR	GA			
			Segment 1	Segment 2	Segment 3	Sum of segments
Backbone	$\frac{1.41}{3.60} = 0.392$	$\frac{1.41}{(1.41+3.08)} = 0.314$	$\frac{(1.41) * \mathbf{0.5}}{(3.60)}$	0	$\frac{(3.60-3.08) * \mathbf{0.5}}{(3.60)}$	0.268
Add-on	$\frac{(3.60-1.41)}{3.60} = 0.608$	$\frac{3.08}{(1.41+3.08)} = 0.686$	$\frac{(1.41) * \mathbf{0.5}}{(3.60)}$	$\frac{(3.08-1.41)}{(3.60)}$	$\frac{(3.60-3.08) * \mathbf{0.5}}{(3.60)}$	0.732

*In the formulae for value attribution shares in GA, **numbers in bold** represent a balance of market power between backbone and add-on*

Unlike the other frameworks, the GA is a symmetric framework that reflects the contributions of both the add-on and backbone, regardless of any first-mover advantage, and the CT IE into the value share attribution, ensuring that the value shares proportionately reflect each constituent's contribution across all degrees of additivity (Towse et al., 2022). In Figure 1, the value of the CT is considered in three segments:

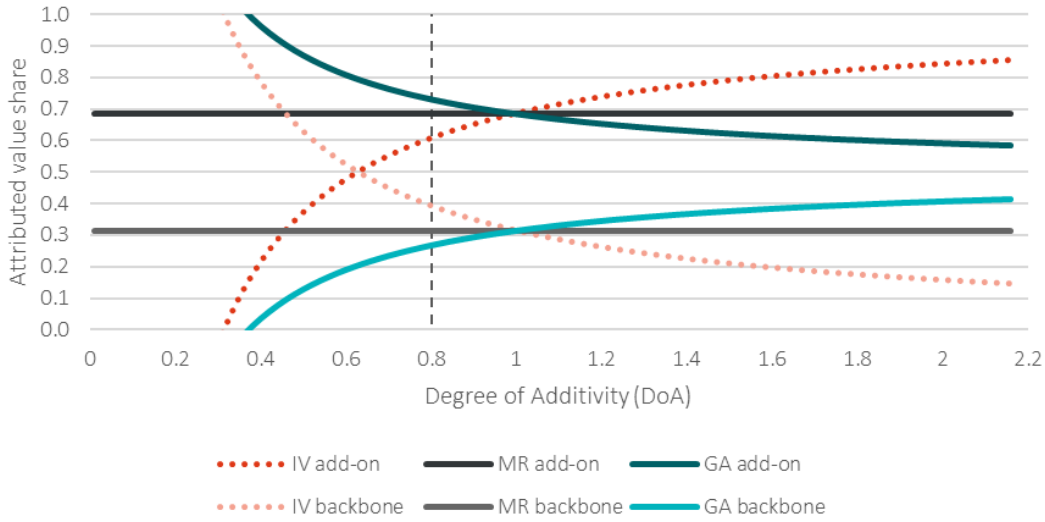
- *Segment 1:* Represents value contributed by both therapies. It goes up to the less effective therapy's monotherapy effectiveness estimate. Under balanced market power, this value is shared equally.
- *Segment 2:* Reflects the value contributed by the more effective therapy, attributed 100% to that therapy. This represents the difference between the more effective therapy's monotherapy effectiveness estimate and the less effective therapy's monotherapy effectiveness estimate.
- *Segment 3:* Represents additional value contributed by both therapies to the CT IE beyond their individual monotherapy estimates. This value is shared equally under balanced market power.

Using the GA, the value shares for the backbone and the add-on are 0.268 and 0.732, respectively. This approach provides value shares informed by more of the relevant IE estimates compared to the IV and MR approaches.

1.1.2 Scale of additivity

Figure 2 shows how each framework attributes value under different additivity scenarios for the worked example described above. We hold the incremental health gain of B and A fixed and vary C such that the incremental health gain of the CT is equal to (CAS), less than (SubAS) or greater than (SuperAS) the sum of the monotherapy IE estimates of the B and A relative to SOC:

FIGURE 2 VALUE ATTRIBUTION SHARES FOR QALY ESTIMATES FROM NICE TA400 AND TA384



The Black dashed line represents the degree of additivity for the QALY estimates from NICE TA400 and TA384.

Constant Additivity Scenario: Under constant additivity, all approaches yield equal value shares for the constituent therapies. However, constant additivity is not always observed in practice, and SubAS is likely to be more common.

Subadditive Scenario: The GA attributes value by considering both monotherapy IE estimates and the combination IE. In the example provided, the add-on therapy is more effective as a monotherapy than the backbone, so the add-on receives a share of all value segments. As the DoA decreases, the shared value in Segment 3 diminishes, reducing the absolute value attributed to both therapies, but the backbone's value declines more significantly than the add-on's. Thus, the backbone's value share decreases while the add-on's share increases.

This contrasts with the IV approach, where the backbone's market power anchors its value in the CT to its monotherapy value. Here, a lower degree of additivity increases the backbone's value share as a proportion of the total CT value. For example, when the DoA is <0.6, the IV approach gives the backbone a larger value share despite the add-on's greater monotherapy IE.

The MR approach maintains constant value shares across all DoA because it does not consider the combination IE in calculating value shares. This approach uses both monotherapy estimates, thus assigning the larger value share to the add-on due to its higher monotherapy IE.

Superadditive Scenario: In SuperAS, when the DoA exceeds 0.6, the add-on receives the majority of the value, disproportionately reflecting its contribution to the combination. Using the GA, the add-on gets the majority of the value at all DoA due to its higher monotherapy IE. However, as the DoA increases, the add-on's value share decreases while the backbone's share increases because of the increased shared value in Segment 3.

Using the IV approach, a higher DoA reduces the backbone's value as a proportion of the total CT value, due to the anchoring of the backbone's value in the CT to its monotherapy value.

As noted with the CAS and SubAS scenarios, the MR approach returns the same value shares across all DoA as the derivation of shares does not take into account the IE of the CT.

1.1.3 Market Power Balance

Market power is an important commercial consideration for companies when allowed to negotiate value shares of the backbone and the add-on in the combination. Market power may also come into play when the value-based price of the backbone is considered fixed by payers, e.g. when multi-incident pricing is not allowed or when decision-makers have other reasons to treat the backbone differently from the add-on (e.g. rewarding early innovators or new entrants).

With balanced market power between backbone and add-on manufacturers, the MR and GA frameworks are symmetric, basing value shares on the monotherapy IE of the constituents. In practice, the backbone therapy often has a first-mover advantage, allowing it to anchor the value (and price) in the CT to its monotherapy value, as seen in the IV approach.

The MR and GA frameworks can adapt to different market power balances. As described by Briggs et al. (2021), when market power favours the backbone (i.e., greater than 50%), the backbone manufacturer can negotiate for the higher share attributed by either the MR or IV framework, with the add-on manufacturer receiving the residual value.

In the GA framework, the balance of market power influences the proportion of shared value segments (Segments 1 and 3) attributed to the backbone. When market power favours the backbone, its value attribution share increases due to capturing a larger portion of Segments 1 and 3, thereby decreasing the add-on's share.

Table 4 in the appendix displays value attribution formulae for each approach under scenarios of balanced and imbalanced market power.

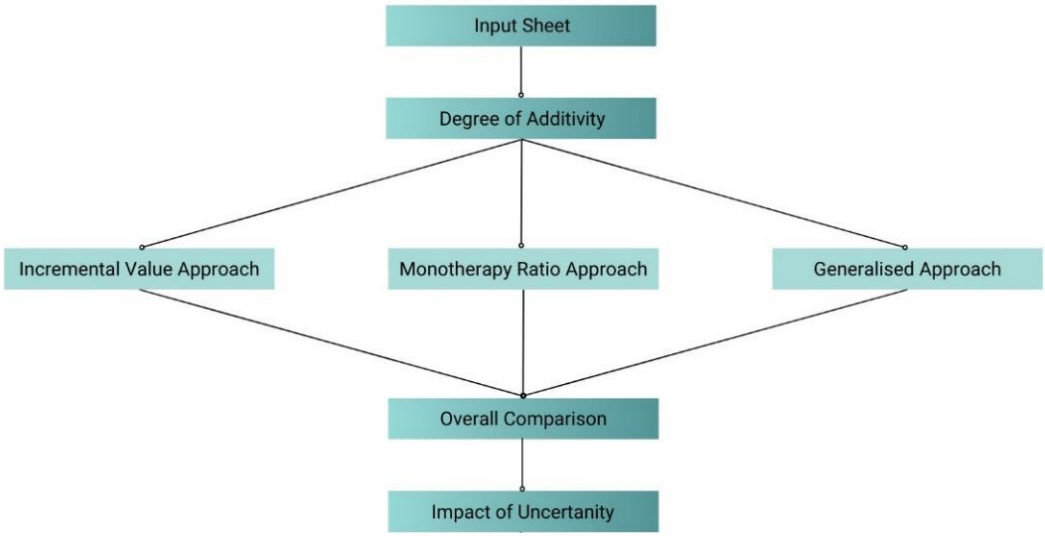
VAF survey and user-tool

In light of the discourse around the challenges in access to CTs and the proposals for the MR and GA frameworks (Latimer et al., 2021; Towse et al., 2022; Briggs et al., 2021), we conducted a study to gather industry insights on the comparative strengths and weaknesses of the three VAFs. To facilitate this, we developed a tool that enabled an expert project team, convened by the ABPI, to apply the frameworks to their internal company case studies. We then created and administered a qualitative survey to assess their perceptions and experiences with various aspects of the frameworks, as well as the usability of the tool.

1.2 Value attribution tool

The value attribution tool (Figure 3 Schematic of value attribution toolFigure 3) was designed in Excel® to derive and compare the value shares for the components of a CT across the three VAFs.

FIGURE 3 SCHEMATIC OF VALUE ATTRIBUTION TOOL



Starting with the "Input sheet", the user can enter values for the IE estimates for the backbone, add-on and CT relative to SOC, the range of plausible values for the add-on and CT, and the market power of the backbone relative to the add-on therapy. Next, the "Degree of Additivity" sheet describes and demonstrates CAS, SubAS and SuperAS using the input values.

The inputs to and results for each VAF are shown separately on the "Incremental Value Approach", "Monotherapy Ratio Approach" and "Generalised Approach" sheets. The sheets display the value attribution shares and attribution of the incremental health gain in a bar chart for each VAF. There is an option for the user to vary the CT IE (thereby changing the DoA) and market power of the backbone to see the impact on the value shares generated.

Results of all three VAFs are shown side-by-side on the "Overall Comparison" sheet. The impact of varying the plausible range of input values for the CT and the add-on can be explored on the "Impact of Uncertainty" sheet.

A "Triplet Combination" sheet (not shown in Figure 3) allows the generation of value attribution shares with the MR and GA approach for CTs with three components.

1.3 Qualitative survey

We developed a qualitative survey including ranking, scoring and open-ended questions. These were sorted into the following sections:

1. *Usefulness of VAFs:* to understand perceptions around perceived fairness of value attribution shares, feasibility of use and potential for overcoming perverse cost-effectiveness issues like the NCZP problem
2. *Estimating monotherapy IE of backbone and add-on*: difficulty of obtaining estimates and potential sources
3. *Use of VAFs in HTA*: factors affecting engagement and uptake
4. *Additional considerations for triplet combinations*
5. *Ease of model use*: feedback on the user experience of the tool
6. *Other comments*: an opportunity for any other comments on the VAFs and the tool

The full list of questions can be found in the appendix.

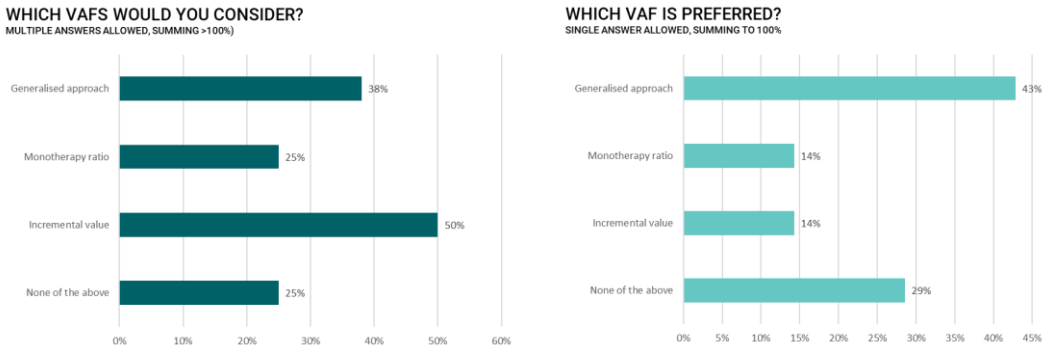
The survey was administered to individual members of the ABPI combination therapies project team (n=10), representing multiple pharmaceutical companies with backbone and/or add-on therapies in their product portfolio or pipeline (therefore potentially facing different market power situations). Once all responses were gathered, the results were analysed descriptively to draw out the key themes of the industry representatives' perceptions of VAFs.

3 An industry perspective of VAFs

Nine of the ten project team members provided feedback on the VAFs and on the use of the tool to aid their understanding and generation of value shares. They found the value attribution tool easy to use and helped to understand "the mechanics" of each VAF under various additivity scenarios and levels of uncertainty. Respondents particularly appreciated that the tool allowed them to compare results across frameworks and that this could help to objectively inform arbitration processes.

When asked to indicate which frameworks they would consider using (multiple answers allowed), half of the respondents selected the IV approach (which is the status quo), 38% the GA and 25% the MR (Figure 4, L-hand panel). Free text responses showed that practical implementation issues informed these choices. When limited to one choice, the GA was the most preferred VAF with 43% of the votes (Figure 4, R-hand panel), followed by "none of the above" (26%).

FIGURE 4 PREFERENCES FOR VAFS



These results indicate that there is no single ideal solution and that each VAF has its strengths and weaknesses as well as opportunities and barriers to implementation.

3.1 Strengths and weaknesses of VAFs

An overview of the strengths and weaknesses of each VAF is provided in Table 2. We discuss below the most salient findings from the survey.

TABLE 2 STRENGTHS AND WEAKNESS OF VAFS

Strengths and weaknesses of VAFs	IV	MR	GA
Perceived fairness of value attribution shares	Does not fairly reflect value if sub- or super-additivity	Does not fairly reflect value if sub- or super-additivity	Perceived to be fair across all scales of additivity
Feasibility of use	Status quo, partial information	Full information required	Full information required
Uncertainty of inputs and outputs	Backbone and CT IE are likely to be available	Uncertainty due to no/limited data on add-on IE	Uncertainty due to no/limited data on add-on IE
Accuracy under sub- or super-additivity	Technically incorrect	Technically incorrect	Technically correct

Notes: Green = strength of VAF; Orange = limitation

3.1.1 Perceived fairness of value attribution shares

Perceived fairness of attribution shares	Generalised Approach > Monotherapy Ratio > Incremental Value

When asked about the perceived fairness of each of the approaches, 67% of respondents ranked the GA first, and 33% ranked it second. Free text answers indicated this is because the GA symmetrically attributes value to the backbone and add-on in relation to the overall CT value across various possible additivity scenarios.

The MR approach sat in the middle, with 66% of respondents ranking it second and 11% ranking it first. Respondents noted that it produces values similar to the GA, especially when the overall CT value is close to what would be expected under constant additivity. Yet by ignoring actual overall CT value, especially under sub- or super-additivity, it was perceived as potentially unfair when the mode of action for the backbone and add-on would "activate" the other treatment to deliver overall CT value greater than the (sum of the) individual monotherapies.

Respondents perceived the IV approach as the least fair (78%) because it may give too much of an advantage to the backbone therapy as the first mover.

3.1.2 Feasibility of use

Feasibility of use	Incremental Value > Monotherapy Ratio > Generalised Approach

The IV approach was almost unanimously ranked as the most feasible to use by 88% of respondents, based on the simplicity of the approach, the partial information evidence requirements and the long precedent of use as the status quo approach to value attribution. The average ranking of the MR approach was slightly higher than the GA. Feedback from respondents indicated this could be a result of the GA being seen as more computationally complex.

While the MR approach and GA were largely considered to have similar levels of feasibility regarding their requirement for full information to generate value attribution shares, participants highlighted that it is unlikely that this information would be readily available. In contrast, the IV approach requires only partial information, in the form of the IE estimates of the combination and only one of the monotherapy IE estimates.

3.1.3 Uncertainty around inputs and outputs of the VAF

Uncertainty around inputs and hence outputs was considered a significant disadvantage of the GA and MR approach. While estimating the IE of the backbone monotherapy in the population indicated for the combination therapy should be feasible, there is likely no direct evidence of add-on monotherapy IE.

When an add-on has been developed solely to work within a combination therapy, it is unlikely that an appropriate head-to-head trial relevant to the decision problem exists. Other suggested sources of information for add-on monotherapy IE included early Phase 1 trials or pharmacokinetic studies, data for a similar treatment in the same class, the target product profile and existing published literature.

Participants also voiced that even if IE estimates exist, they are unlikely to be in the same treatment line or against a common SoC, which may evolve rapidly in some oncology indications. While this

might be overcome by comparing to a different common comparator, additional analyses would be required to generate such indirect treatment effects.

Methods for structured expert elicitation (SEE), e.g. the 'chip and bin' method (Horscroft et al., 2023; Soares et al., 2018; Bojke et al., 2022) were also mentioned to generate estimates for the add-on as monotherapy and quantify uncertainty. However, respondents deemed SEE to be onerous to conduct with multiple healthcare professionals and potentially subject to mistrust by other manufacturers.

Respondents perceived the challenges with data availability and uncertainty to compound when applying the MR and GA VAFs to triplet combinations, further reducing the feasibility of these frameworks.

3.1.4 Accuracy under sub- and super additivity

Respondents acknowledged that only the GA is technically correct under non-constant additivity scenarios, but considered its higher computational complexity and need for full information as a trade-off, especially when the overall CT value was expected to be close to constant additivity.

3.2 Opportunities and barriers to implementation

The main implementation barriers and opportunities for each VAF are provided in Table 3, and discussed below in further detail.

TABLE 3 STRENGTHS AND WEAKNESSES OF VAFS

Opportunities and barriers to implementation	IV	MR	GA
Challenges in cost-effectiveness assessment	NCZP problem due to anchored backbone value	Expected to overcome NCZP problem	Expected to overcome NCZP problem
Acceptance of VAFs by payers and decision-makers	Yes – status quo	Unclear	Complexity of GA relative to other VAFs
Inter-company dialogue	Not required	Required – to be addressed by CMA prioritisation statement	Required – to be addressed by CMA prioritisation statement
Commercial implications	Not considered except for imbalance in market power		
Agenda of VAF user	The identity of user may influence choice of VAF		

Notes: Green = strength of VAF; Orange = limitation; Grey = unclear/impact remains to be seen

3.2.1 Challenges in cost-effectiveness assessment

The predominant cost-effectiveness challenge for CTs is the NCZP problem for the add-on when the backbone price is fixed at its highest cost-effective value, leaving no or little space for the add-on to be priced at levels reflecting its value. Their ability to address this issue was considered a main advantage of the GA and the MR.

A disadvantage of the IV approach raised by participants is the priority it gives to the first mover or backbone treatment. One respondent suggested that the barrier to access for add-on therapies outweighs any advantages concerning the ease of use of the IV framework. One respondent stated that these issues 'effectively prevent innovative combination therapies coming to market'.

3.2.2 Acceptance of VAFs by payers and decision-makers

The IV approach reflects the status quo in value attribution. The uptake of the MR approach and GA are dependent on the acceptance of these frameworks by payers and decision-makers, such as NICE and NHS England.

A concern was raised around the complexity of the GA in comparison to the simplicity of the MR and IV frameworks. Calculation of the GA value shares involves the segmentation of the CT incremental health gain into multiple areas of value that are either unique to or shared amongst CT constituent therapies. Feedback from respondents indicated that there may be challenges in appropriately and intuitively communicating the derivation of value shares to NICE and other payers, given the novelty and complexity of the approach.

3.2.3 Inter-company dialogue

Typically, an advantage of the IV framework is that it does not require discussions of value attribution between CT manufacturers. The need for intercompany dialogue has been a challenge for the MR and GA VAFs and overlaps with the competition law problem. This may be mitigated by the Competition and Markets Authority's (CMA's) 2023 prioritisation statement on not taking enforcement actions concerning commercial negotiations for CTs between competing manufacturers (Competition and Markets Authority, 2023). The impact of the CMA's statement on inter-company dialogue and facilitating access to CTs remains to be seen at the time of publication.

3.2.4 Commercial implications

While the GA and MR frameworks can explicitly accommodate the impact of imbalanced market power, respondents highlighted that other commercial implications, beyond value attribution, are relevant as well for their pricing strategy such as confidential discounts, the impact on acceptable profit margins, loss of exclusivity and the knock-on effect on reimbursable prices in other indications.

3.2.5 Agenda of VAF user

A concern was raised over the agenda of the party generating value attribution shares and their agenda determining the choice of VAF. A manufacturer might prefer the VAF that generates more generous value attribution shares for their product relative to the other CT constituent. Payers may have no preference for a specific framework (as long as the combination delivers value for money in line with their decision criteria), but if they do, there is a chance that their preferred VAF generates value attribution shares that are more challenging for industry to negotiate. Also, the circumstances under which the IV or MR VAFs may be more favourable to one party or another depend on the degree of additivity and the IE inputs. The GA has an advantage over the other frameworks in the sense that the solutions are symmetrical and neutral to each CT constituent across all degrees of additivity.

4 Conclusions

The perception by industry of the VAFs under discussion is that while each approach has strengths and weaknesses, the GA was generally considered as the most appropriate and risk-mitigating approach for a portfolio of products that includes both backbone and add-on therapies. The comparative strengths of the GA relative to the other frameworks were ascribed to its ability to overcome the NCZP problem and its perceived fairness in attributing value in a way that is symmetrical and neutral to each CT across all additivity scales. The main limitation of the GA is the requirement for complete information, the absence of which either impedes the use of the framework or introduces uncertainty into the outputs by approximating the inputs. The MR approach also overcomes the NCZP problem and shares the need for complete information.

There may be circumstances in which other frameworks may be more appropriate to use as the basis of value attribution. For example, in the absence of data on add-on monotherapy IE, the next best approach to value attribution may be to assume constant additivity and apply the MR or IV approaches based on the backbone and CT IE estimates. However, the higher the degree of sub- or super-additivity the more incorrect the IV and MR value attribution shares.

Companies' preferred choice of VAF will be influenced by their acceptance by payers and decision-makers, such as NICE and NHS England. As with the other problems affecting assessment and access to CTs, value attribution is a shared problem that requires the co-creation of solutions with HTA agencies and payers. Analogous to how the CMA's 2023 prioritisation statement will help to address the competition law problem (Competition and Markets Authority, 2023), NICE and NHS England could provide their opinion on the acceptance of the results of these VAFs.

Based on the results of this study, we recommend the GA as the starting point for thinking about value attribution in the arbitration process, especially under scenarios of sub- and super-additivity. The discussion between manufacturers and payers could also be supplemented by the shares generated using the IV and MR approaches.

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6

7 Appendix

7.1 Project team survey questions

1. Usefulness of VAFs
   - 1.1. How do each of the VAFs compare regarding the attribution shares produced and feasibility of use? Rank the VAFs in terms of: [ranking exercise]
   - perceived fairness of attribution shares produced
   - feasibility of use
   - overcoming CE issues

   - 1.2. Please add any additional comments you may have on the ranking exercises here (optional)
   - 1.3. What are the advantages of each VAF? [open-ended free text box for each VAF]
   - 1.4. What are the disadvantages of each VAF? [open-ended free text box for each VAF]
   - 1.5. What do you consider the main challenge for each specific framework to be used in practice? [open-ended free text box for each VAF]

2. Estimating monotherapy effectiveness of backbone and add-on
   - 2.1. In general, how feasible is it to estimate monotherapy effects with any certainty? [0-5 scale, 0 = 'it is not feasible, 3 = 'it is feasible with only some certainty', 5 = 'it is feasible with great certainty']
   - Backbone monotherapy effectiveness
   - Add-on monotherapy effectiveness
   - 2.2. What evidence would you typically expect to be available to estimate monotherapy effects for the add-on? [pick one of 3 options: 1 = 'Direct trial evidence would usually be available', 2 = 'No direct trial evidence, but useful indirect and/or other types of evidence would likely exist', 3 = 'No evidence is likely to be available']
   - 2.3. How well were you able to make credible assumptions about the monotherapy effectiveness of add-on treatments, when using this model? (If you have applied the model for more than one use case, note this in the free-form box. If possible, describe if the answer depends on the product, and which characteristics of the product influence differences between answers.) [0-5 scale, = followed by an open-ended free text box to add information about individual cases].
   - 2.4. What sources of information did you base your assumption on? [open-ended free text]
   - 2.5. How does this influence your acceptance/understanding of the value attributions of each framework? [open-ended free text box]
3. Use in HTA
   - 3.1. Which of the VAFs would you consider using in HTA/combination pricing solutions and why? [multiple choice + free text box]
   - Incremental value approach
   - Monotherapy ratio approach
   - Generalised approach
   - None of the above

   - 3.2. Which VAF would be your preferred choice to use in HTA/combination pricing solutions and why? [one choice only + free text box; give an option for 'none of the above']
   - Incremental value approach
   - Monotherapy ratio approach
   - Generalised approach
   - None of the above

3.3. What limitations do you see within the VAFs that could hinder their uptake by industry/HTA? [multiple choice with free text box for "other characteristics"]

- Ability to obtain the information required
- Complexity
- Uncertainty of inputs and outputs
- Other characteristics of the VAFs not listed above [free text box]

3.4 What external contextual factors would influence the uptake of these frameworks by industry/HTA? [checklist to choose any/all of the below, and an open-ended free text box at the end to capture factors not listed here]

- HTA guidance on which VAF to use
- knock-on effect on reimbursable price in other indications
- knock-on effects on reimbursable prices in other geographic areas, e.g. due to reference pricing
- opportunities to negotiate which VAF to use and methods for implementing the chosen VAF that are compliant with competition law
- other important contextual factors of note not listed above? [free text]

4. Additional considerations for triplet combinations

4.1. What specific considerations are present when applying the frameworks to triplet combinations? [multiple choice, and a free-text box to capture "other considerations"]

i) additional competition law concerns
ii) additional data availability requirements
iii) additional administrative and negotiation costs
iv) additional uncertainty in treatment effectiveness
v) uncertainty over whether a combination duplet SOC should be treated as two separate backbone monotherapies or if the duplet combination effectiveness should be treated as a single backbone
vi) other considerations [free-text]

5. Ease of model use:

5.1. Did the tool help you to understand how the different VAFs compare? [0-5 scale, 0 = 'not at all', 5 = 'very much so']

5.2. Is the tool easy to understand? [0-5 scale, 0 = 'difficult to understand', 5 = 'easy to understand']

5.3. What is your experience with applying this model to products in your company's portfolio? Please do not refer to any academic or commercially confidential information when describing your experience. [open-ended free text]

5.4. Would an improved, beta-version, of this model, be of value to your company or to other stakeholders? [open-ended free text]

5.5. What additional outcome measures beyond the QALY could be included in an improved beta-version of the tool to further support its usefulness? [open-ended free text]

5.6. Do you think further work should be done on VAFs to help take them forward for use in combination pricing solutions? [Yes/no, free-text box for additional comments]

6. Final thoughts

6.1. Do you have any other thoughts on the VAFs or the tool that you would like to share? [open-ended free text]

7.2 Calculation of value attribution shares under a balance of market power scenario

TABLE 4 FORMULAE FOR VALUE ATTRIBUTION SHARES IN EACH VAF

	IV		**MR**		**GA**	
	$V_a(B)$	**$V_a(A)$**	**$V_a(B)$**	**$V_a(A)$**	**$V_a(B)$**	**$V_a(A)$**
Value attribution formula assuming equal market power	H_B/ H_{B+A}	$(H_{B+A}- H_B)/ H_{B+A}$	$H_B/(H_B+H_A)$	$H_A/(H_B+H_A)$	Segment 1: $H_B/(2*H_{B+A})$ + Segment 2: $(H_B -H_A)/ H_{B+A}$ + Segment 3: $(H_{B+A}-H_B)/ (2*H_{B+A})$ = $(H_{B+A}+H_B- H_A)/ (2*H_{B+A})$	Segment 1: $H_A/(2*H_{B+A})$ + Segment 3: $(H_{B+A}-H_B)/ (2*H_{B+A})$ = $(H_{B+A}+H_A- H_B)/ (2*H_{B+A})$
Value attribution formula with imbalanced market power	H_B/ H_{B+A}	$(H_{B+A}- H_B)/ H_{B+A}$	Max(H_B/H_{B+A}, $H_B/(H_B+H_A)$)	Min($(H_{B+A}- H_B)/ H_{B+A}$, $H_A/(H_B+H_A)$)	Segment 1: $(MPB*H_A)/(H_{B+A})$ + Segment 2: $(H_B -H_A)/ H_{B+A}$ + Segment 3: $(MPB*(H_{B+A} -H_B))/ (H_{B+A})$ = $((MPB-1)* H_A + (1- MPB)*H_B + MPB*H_{B+A})/ H_{B+A}$	Segment 1: $((1- MPB)*H_A)/(H_{B+A})$ + Segment 3: $((1-MPB)* (H_{B+A}-H_B))/ (H_{B+A})$ = $((1- MPB)*(H_A+ H_{B+A} - H_B))/ (H_{B+A})$

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