An Attribution of Value Framework for Combination Therapies

Report by the Value Attribution Working Group

January 2021

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Acknowledgements

Development of this Whitepaper was funded by Takeda UK Ltd

The authors are grateful for oversight and comments during the development of this Whitepaper from the following individuals:

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1. Executive Summary

In 2014, the Decision Support Unit (DSU) for the UK National Institute of Health and Care Excellence (NICE) published a working paper that outlined the circumstances in which health technologies that are demonstrated to be effective, may nevertheless be deemed not cost-effective even at a zero price [1]. In particular, the report highlighted that in certain situations it is possible for a treatment combination consisting of a backbone treatment and a novel add-on therapy to fail to be cost-effective even if the price of the add-on treatment equals zero. This can lead to the add-on therapy within a combination not having a recommendation at the end of a lengthy appraisal and negotiation process, or manufacturers taking the decision to not enter the appraisal process at all despite evidence of clinical efficacy.

The crux of the issue stems from combination treatments being evaluated as single technologies but composed of component treatments that are each priced independently. The initial entrant to the market, commonly referred to as the "backbone treatment", has the entire willingness-to-pay (WTP) threshold to work with and once assessed and recommended is unlikely to be reassessed. Since the overall cost of the treatment combination includes both components, the add-on component of a combination therapy, by contrast, has a much-reduced opportunity to demonstrate value. Furthermore, if the component treatments are manufactured by different companies, they cannot discuss and re-align prices since this is prohibited by anti-trust law. Therefore, manufacturers of the add-on therapy only have control over the price of their own products and not the overall cost of the treatment combination. Since the publication of the DSU report in 2014 the issue surrounding how to assess combination treatments has been discussed and debated, but with few tangible and workable solutions documented.

In November 2019, the Bellberry Group convened a three-day international workshop, inviting experts representing all relevant stakeholders from around the world to discuss the challenges associated with valuing and paying for treatment combinations in oncology. In their discussions, which included input from HTA representatives, academia, industry and wider stakeholders, there was support for flexible payment systems and pricing, including potential re-assessment of the backbone therapy by Health Technology Assessment (HTA) agencies and re-visitation of the prices of component treatments. Addressing the question of how the price reduction should be shared requires an accepted method for determining how much of the value of a combination treatment should be attributed to each of its component treatments. The participants at the Bellberry workshop highlighted a need for dedicated research on methods of value attribution [2].

Taken together, it is clear that all stakeholders: government, HTA bodies, payers, and manufacturers, agree that a fair, implementable and transactable solution needs to be found. Takeda UK Ltd has been looking into this issue for several years; they held a parliamentary roundtable in 2016 and has had ongoing discussions with stakeholders on a number of topics raised. In 2019, Takeda established an Advisory Panel that was tasked with designing transactable and implementable solutions to the problem

of assessing combination treatments. The group was made up of experts from HTA, National Health Service England (NHSE) commercial and commissioning, clinical practice, pricing & competition, health economics and patient organisations. These advisors split proposed solutions into two distinct interlinking activities:

1. An Attribution of Value Framework to assign a specific value to each combination treatment

2. A Conceptual Framework and Standard Operating Procedure for an arbitration process which considers competition law

In this Whitepaper, the results of the first workstream for attributing value to the components of a combination treatment are reported. An accompanying Whitepaper addressing the second workstream on voluntary arbitration will be published shortly.

The proposed value attribution methodology is explored through four scenarios which are characterised by key features of the problem: perfect/imperfect information about the monotherapy effect of component treatments and balanced/unbalanced market power between their manufacturers. The proposed solutions are grounded in the standard rules of cost-effectiveness and designed to make use of the same information that NICE uses to undertake its appraisals of technologies. One advantage of the proposed framework is that it is independent of price and focuses on the (value of) Quality Adjusted Life Year (QALY), the standard metric by which NICE, and many other HTA agencies, compare the health benefits of different treatments. In addition, case studies are employed to demonstrate how implementable the proposed solutions could be based on publicly available information for some treatment combinations which have previously been appraised by NICE.

The Attribution of Value Framework described is meant to serve as a preliminary structure to facilitate discussion and debate among stakeholders. The proposed framework is grounded in careful review of the challenges to valuing and pricing combination treatments and has been developed over time with input from the Advisory Panel. This work aims to advance the objective of researching and developing methods of value attribution that was set forth at the Bellberry workshop [2] and supports efforts to ensure that patients have access to clinically important treatments as rapidly as possible.

2. Introduction

The use of combination therapies has been increasing over time with greater scientific understanding of the complex pathophysiology of disease progression. As combination therapies can target multiple pathways and levels of a disease simultaneously, they often exhibit greater clinical efficacy than single-agent therapies [3,4]. This has been evident in the treatment of HIV infection, for example, where standard use of antiretroviral combination therapies has reduced rates of disease transmission and increased patient life expectancy [5, 6]. Combination therapies have also emerged as mainstay treatments in the field of oncology. Treatment with multiple agents often generates a higher therapeutic response and better outcomes for cancer patients [7]. Yet despite their known clinical benefits, value assessment of novel combination therapies using conventional methods has proved challenging. This can cause combination therapies to receive a 'not recommended' decision and may discourage manufacturers from making HTA submissions of combination therapies. As a result, patients could be unable to access innovative therapies which could bring substantial clinical benefits.

While combination therapies in many disease areas share features that make it more difficult to demonstrate economic value under existing valuation frameworks, it has been especially challenging for combination therapies in oncology. Thus, although much of the discussion that follows will be relevant to combination therapies in many fields, this paper focuses on the value assessment of combination therapies in oncology.

A key challenge to value assessment is that a treatment combination is evaluated as a single technology, but the component therapies are priced independently. The situation is made more difficult when the component therapies that form a combination are patented and produced by different manufacturers. Manufacturers have control over the price of their own product(s) but not over the overall price of the combination. The economic evaluation challenge of combination medicines was discussed in a report by the NICE Decision Support Unit (DSU) which highlighted how combination medicines can fail to be cost-effective even if the novel add-on therapy is provided at zero cost [1]. Within the field of oncology, this scenario often arises where a clinically effective combination therapy is administered until disease progression, so if the combination improves progression-free survival it will lengthen the duration of both the backbone and add-on treatment. Even if the cost of the add-on therapy equals zero, the total cost of treatment will increase because patients will be treated with the existing backbone therapy for longer. We describe these challenges in more detail in the sections that follow together with proposed solutions to the problem that the DSU has highlighted.

A group of international stakeholders and experts in health technology assessment outlined key challenges and potential solutions to valuing and paying for combination therapies in oncology at an international workshop hosted by Bellberry in 2019 [2]. Stakeholders included HTA agency staff, clinicians, academics, patient representatives, and pharmaceutical industry personnel. The ideas that emerged from this workshop thus reflect a diverse set of perspectives. There was unanimous recognition of the issue that combination medicines present to health technology appraisals and the

need to find a solution. In addition, there was broad support for flexible payment systems and pricing, which were believed to be the most implementable solutions in the near term. The proposed solutions included potential re-assessment of the backbone therapy by HTA agencies and payers and re-visitation of the prices of component therapies by their respective manufacturers. Participants emphasised that implementation of such solutions requires an accepted method for attributing the value of a combination to its component therapies. They asserted that there was a need for dedicated research on methods of value attribution, and that such research should involve a wide variety of stakeholders.

Despite the wide recognition of the issue and the need for a solution, to date, no solution has been proposed to address the valuation of component therapies of a combination for a number of reasons. It is difficult to demarcate the marginal contributions of individual component therapies even when their monotherapy effects are known since the outcomes generated by the combination are the product of unobservable and potentially synergistic pharmacological processes and drug interactivity [3, 8]. Furthermore, when component therapies are developed specifically to be used in combination with existing therapies, such therapies may not have been clinically evaluated independently outside of early phase safety and dose escalation trials. This poses an additional challenge to value attribution since the monotherapy effect of component therapies will be uncertain as well [9].

In this paper, we propose an Attribution of Value Framework for combination therapies. The framework provides a structured method for determining how to attribute the benefit of a combination therapy to each of its component therapies. The proposed framework is grounded in careful review of the challenges of valuing and pricing combination therapies and has been developed over time with input from the Advisory Panel consisting of a broad spectrum of stakeholders, including HTA staff, clinicians, academics, and pharmaceutical company personnel. This work thus advances the objective of researching and developing methods of value attribution that was set forth at the Bellberry workshop by presenting a possible solution. The goal of the paper is to facilitate discussion among stakeholders—such as HTA agencies, manufacturers, and payers—who must work together to ensure that these therapies are available and accessible to the patients who benefit from their use.

In the next section we present the background to the problem. Section 4 then lays out the framework we propose for the basis of negotiations between stakeholders and Section 5 presents a series of case studies. A final section offers a discussion of the issues.

3. Background

3.1. Definition of combination therapies

A combination therapy combines two or more individual component therapies to treat a single disease. Many combination therapies are comprised of a "backbone" therapy and one or more "add-on" therapies. A backbone therapy is a drug or drug combination that is already approved for use and whose market share and use in clinical practice is well-established prior to it being used in combination with another therapy. These backbone therapies are often the existing standard of care for a given disease. An add-on therapy is a drug or set of drugs that is added to an existing backbone therapy. This therapy may have been developed and introduced into the market as an independent therapy, or it may have been developed specifically to work in combination with the backbone therapy. In the latter case, the clinical development program and registrational trials would likely have been conducted with the combination regimen only. We note that a combination therapy that includes an add-on therapy can become a backbone therapy as the standard of care changes over time.

Combination therapies may exhibit greater clinical efficacy than single-agent therapies when their component therapies have complementary or synergistic pharmacodynamic effects. Component therapies often generate better health outcomes when used in combination because they target different receptors and pathophysiological pathways of a disease. For example, pertuzumab and trastuzumab, both immunotherapy agents, each bind to different human epidermal growth factor receptor 2 (HER2) epitopes. Their combined use thus provides dual blockade of HER2 signalling pathways, which showed interim improved survival for patients [10]. Similarly, combination therapies may generate better health outcomes because the activity of one component therapy potentiates the activity of another. In another example, research suggests that pembrolizumab (another immunotherapy agent) may potentiate the effect of pemetrexed-platinum (a doublet chemotherapy) and thereby enhance anti-tumour activity when they are used in combination to treat programmed death-ligand 1 (PD-L1) positive advanced or metastatic non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations [11].

3.2. Economic evaluation of combination therapies

Novel therapies and technologies are subject to rigorous economic assessment to optimise the allocation of finite healthcare budgets. One method that is commonly used to assess the economic value of new therapies is cost-effectiveness analysis (CEA). This approach assesses value based on how changes in healthcare costs correlate to changes in health outcomes. The quality-adjusted life year (QALY) is the standard outcome measure that is used in CEA. Use of the QALY makes it possible to compare healthcare interventions based on a common measure of value across different therapy areas. Currently, HTA agencies evaluate combination therapies as single technologies using the same methods

used to evaluate monotherapies. Yet there are systemic factors that make it difficult for combination therapies to achieve cost-effectiveness when applying conventional CEA methods.

A feature of combination drugs that influences the results of CEAs is that component therapies are often patented therapies with a higher price. Adding a costly novel drug to an already expensive drug or drug combination increases drug acquisition costs significantly. Since all therapies are evaluated at the same willingness-to-pay (WTP) threshold, the combined costs of two or more patented therapies will often exceed the WTP for a given health benefit. In a scenario where a novel add-on therapy is combined with an existing backbone therapy, the manufacturer of the add-on therapy will only have control over the price of its own product and not the overall combination. The existing backbone therapy will already have gone through the appraisal process and have a set price. Furthermore, the price of the existing backbone therapy may already be set close to the WTP for its associated health benefits. This leaves little room for the additional cost of the add-on therapy and may prohibit innovation.

The report by the NICE Decision Support Unit (DSU) demonstrated that it is possible for a combination therapy consisting of an existing backbone therapy and a novel add-on to fail to be cost-effective even if the add-on therapy is provided for free [1, 12]. In oncology, patients are commonly treated until disease progression occurs. Thus, if a novel combination therapy consisting of two or more patented drugs delays disease progression, patients are treated with both costly drugs for a longer duration of time [1, 12]. This is the most common reason why novel cancer combination therapies fail to achieve cost-effectiveness, as many treatments are administered in a treat-to-progression approach. The DSU showed that, even if the price of the add-on therapy equals zero, the longer duration of treatment with the backbone drug increases the total cost of treatment with the combination therapy. The DSU similarly showed that if a combination therapy lengthens the amount of time that patients spend in a post-progression state, patients receive best supportive care for a longer duration of time and thereby incur additional costs [1, 12]. As a result of this perverse relationship between gains in survival and costs, clinically beneficial combination therapies may not be cost-effective even when the novel add-on therapy is provided for free [1, 12].

The challenges described above are exacerbated when the backbone therapy meets end-of-life criteria at the time of its appraisal, but the combination therapy does not similarly qualify. This scenario may arise because life-expectancy prior to the introduction of the backbone therapy was lower than the time typically considered end-of-life, but the introduction of the backbone therapy into clinical practice has considerably improved life expectancy, meaning that the population no longer meets the end-of-life criteria. In these cases, the price of the backbone therapy will be set based on the higher WTP threshold that is applied to end-of-life treatments. This makes it especially challenging for a combination therapy to be considered cost-effective at the standard WTP threshold since there is even less room for the additional cost of the add-on therapy. Thus, there are many distinct issues that arise when assessing the value of combination therapies.

These issues with CEA of combination medicines and the lack of appropriate methods to address the attribution of value may discourage HTA submissions of effective novel combination therapies. As a result, patients could be unable to access clinically important innovative therapies and there remains an urgent need as a community to develop solutions.

3.3. The value attribution problem

Combination therapies are clinically important for the treatment of diseases with complex pathophysiological processes such as cancer. For patients to have access to these beneficial treatments, combination therapies must be priced commensurately with their value as measured by accepted WTP. Yet when combination therapies are composed of individual drugs that are priced independently, the cost of the combination may, for the reasons described in section 4.2.2, exceed its value-based price. This occurs because: 1) the prices of component therapies that have already been approved will have been set without consideration of the total cost of the combination, and; 2) WTP for the incremental benefits generated by the combination is often absorbed by a corresponding increase in the cost of the backbone therapy as described in the previous section.

The prices of component drugs must therefore be reduced for the combination therapy to be cost-effective. To address the question of how the cost reduction should be shared, we must determine how much of the value of the combination therapy should be attributed to each of its component therapies.

A desirable value attribution strategy would attribute value to each component therapy based on its marginal contribution to the health outcome generated by the combination. However, these marginal contributions are often difficult to quantify. Practical implementation is further hampered as even the independent clinical benefits of component therapies are often unknown. Value attribution is also more difficult when component therapies are produced by different manufacturers since any imbalance in market power creates potential "winners" and "losers" (either compared to the status quo or indeed to a perception of what could be achieved). In the case of a combination therapy that is formed by combining an existing backbone therapy with a novel add-on, the balance of power will often be tilted towards the manufacturer of the backbone therapy. This occurs in part because combination therapy and its backbone therapy are appraised independently. Once an existing backbone therapy has been appraised and approved by an HTA, it is not likely to be re-assessed. The appraisal of the combination therapy will be fully sponsored by the manufacturer of the add-on therapy. The manufacturer of the existing backbone therapy thus has a reduced incentive to revisit the price of its own product and participate in negotiations related to value attribution.

In the sub-sections below, we discuss in more detail these two defining features of the value attribution problem: 1) imperfect information and 2) imbalance of market power.

3.3.1. *Imperfect information*

The health outcome generated by a combination therapy is the product of pharmacodynamic or, more rarely, pharmacokinetic interactions. Thus, the extent to which component therapies independently contribute to the observed health outcome is unknown. In some cases, component therapies will have been studied independently in phase III clinical trials. In these cases, we still will not know the extent to which each therapy contributes to the outcome generated by the combination therapy. However, we can use what we know about the health benefits generated by each therapy independently to apportion the value derived from the combination therapy. In many cases, however, the independent value of component therapies will not be known. Many therapies are developed specifically to work in tandem with another therapy and as such may be authorised for use only within the combination.[1] With the possible exception of early-stage clinical studies to establish the pharmacodynamic properties of the drug and the essential information to support its future therapeutic use (indication, dose and tolerability for example), add-on therapies are often only studied in combination with the backbone therapy. We use the term "imperfect information" to define scenarios where the independent benefit of one or more of the component therapies is unknown for the indication under consideration. Imperfect information scenarios typically arise when a novel add-on is combined with an existing backbone therapy. In contrast, we use the term "perfect information" to define scenarios where the independent benefit of every component benefit is known for the indication for which the combination therapy is being assessed. Perfect information scenarios typically arise when a combination therapy is composed of two existing therapies that have already been appraised and approved independently. It is more difficult to solve the value attribution problem in scenarios where there is imperfect information.

3.3.2. *Imbalance of market power*

Given that the WTP ceiling is often the same regardless of regimens being monotherapies or combinations, the price of the backbone therapy may need to be reduced to establish prices for add-on therapies that are commensurate with their value. As discussed previously, a backbone therapy that has already been appraised will be priced near the WTP threshold for the health benefit it generates. There is thus little room for innovation and the additional cost of an add-on therapy if the same WTP threshold is applied to the cost of the combination.

The degree to which price coordination is possible depends on whether component therapies are produced by one or several manufacturers. When all the component therapies are produced by a single manufacturer, the manufacturer has full control over pricing decisions. Furthermore, the manufacturer has access to relevant information about each of the therapies, such as forecasted sales volumes, which it can use to optimise pricing. [7].

[1] Although this paper focuses on the case where component therapies are pharmaceuticals, this is true of other types of medical interventions as well. Medical devices and companion diagnostics, for example, are often developed to guide and monitor treatment with a specific drug therapy.

Price coordination must take into consideration anti-competition laws when component therapies are produced by different manufacturers. Antitrust regulation prohibits different manufacturers from working together explicitly to make pricing decisions [3, 9]. Thus, in this situation the manufacturer of the add-on therapy must devise a pricing strategy without knowing the pricing strategy of the manufacturer of the backbone therapy [7]. Flexibility in the pricing of the backbone therapy will depend on its current stage in the product life cycle as well as whether it remains under patent and for how long. If a backbone therapy has many years left under patent or holds sufficiently large market share, its manufacturer may have little incentive to reduce its price.

The feasibility of flexible pricing will also depend on the local market construct. Different jurisdictions may not allow for indication specific discounts or the variation of prices across indications. Any reduction in price will reduce revenue across all indications. If a backbone therapy is approved for multiple indications, and the market does not allow price or discount variation by indication, its manufacturer may have little incentive to reduce its price. The manufacturer of the add-on therapy may be forced into setting a lower price so that the combination therapy will be cost-effective as a result. In this scenario, the manufacturer of the add-on therapy bears the full cost of developing the combination therapy but captures limited value [3, 8]. In contrast, the manufacturer of the backbone therapy captures additional value from the combination therapy without bearing new costs. When the backbone therapy is an established therapy while the add-on is a new market entrant, many novel combination therapies will fail to demonstrate cost-effectiveness. This reduces patient access to clinically important combination therapies in markets where cost-effectiveness is the route to reimbursement [3].

We use the term "imbalanced market power" to define scenarios where the manufacturer of one component therapy has more control over pricing decisions compared to the manufacturer of another component therapy. There will typically be an imbalance of market power when a novel add-on is combined with an existing backbone therapy that has already been appraised and approved. Additionally, there can be an imbalance of market power when each of the component therapies has been appraised and approved, but one of the component therapies holds a larger share of the market—either in the indication for which the combination is being appraised or across multiple indications—than another component therapy. We use the term "balanced market power" to define scenarios where none of the component therapy manufacturers has more control over pricing decisions than another. Market power will often be balanced in cases where a combination therapy consists of two or more existing therapies that have already been appraised and approved and there is no large discrepancy in their respective market shares.

4. Attribution of Value Framework

In this section we lay out the proposed Attribution of Value Framework. We start from the standard rules of cost-effectiveness analysis and we assume that the value of the combination therapy can be determined. We then go on to define the problem in terms of whether component treatments are sub-additive or synergistic. Finally, we propose potential solutions to each of four scenarios defined by the information available (perfect/imperfect) and the balance of power between manufacturers (balanced/imbalanced).

4.1. Standard rules of cost-effectiveness analysis

Standard health economic decision rules dictate that an intervention should be implemented over a comparator if its incremental health benefits justify its incremental costs [13]. When incremental costs are negative and incremental benefits are positive, the treatment is considered 'cost-saving' and should be implemented. When incremental costs are positive and incremental benefits are negative, the treatment is 'dominated' and should not be implemented. When incremental costs and benefits are both positive or both negative, decision-makers must consider the value of the treatment in terms of the ratio of the additional costs relative to the additional benefits.

The incremental cost-effectiveness ratio (ICER) is the statistic that is used to summarise this value and is defined as the incremental costs (ΔC) divided by incremental benefits (ΔE). When QALYs are employed as the measure of health benefit in cost-effectiveness analysis, ICERs represent the cost-per-QALY gained attributable to implementing a treatment versus its comparator. Value for money is assessed by comparing the ICER statistic to a maximum willingness-to-pay (WTP) for an additional QALY represented by the decision-maker's cost-effectiveness threshold, λ. This 'decision rule' for cost-effectiveness can be represented as an inequality with the decision to implement a new treatment supported if its ICER falls below the threshold:

$$\frac{\Delta C}{\Delta E} < \lambda.$$

This decision rule can be rearranged to define an equivalent decision rule in terms of incremental net health benefit (Δ*NHB*) [14] whereby the new technology is adopted if its ΔNHB is greater than zero.

$$\Delta NHB = \Delta E - \frac{\Delta C}{\lambda} > 0.$$

Weinstein and Stason describe how the incremental costs and effects attributable to implementing a health care intervention compared to a relevant comparator can be disaggregated into constituent parts [15]:

$$\Delta C = \Delta C_{rx} + \Delta C_{se} - \Delta C_{morb} + \Delta C_{le}$$

$$\Delta E = \Delta E_{le} + \Delta E_{morb} - \Delta E_{se}$$

The constituent parts of incremental costs (ΔC) are those differences attributable to treatment cost (rx), treatment-related side-effects (se), reduced morbidity of the disease (morb) and increased life-expectancy (le). The constituent parts attributable to the incremental QALYs (ΔE) are the difference in QALYs due to increased life-expectancy (le), reduced morbidity of disease (morb) and reduction in quality of life due to side-effects (se).

Substituting these components into the inequality for the ΔNHB decision rule generates a further (equivalent) interpretation of the decision rule: that the new treatment will only be considered cost-effective if the additional benefits of the new treatment (net of differences in the QALY equivalent values of any cost-savings) outweigh the additional cost of the new treatment (also expressed as a QALY equivalent)

$$net\Delta Q = (\Delta E_{le} + \Delta E_{morb} - \Delta E_{se}) - \frac{(\Delta C_{se} - \Delta C_{morb} + \Delta C_{le})}{\lambda} > \frac{\Delta C_{rx}}{\lambda}.$$

The importance of this derivation of the decision rule is that the left-hand side of the inequality expresses the value of the new intervention in terms of its (net) impact on health (measured in terms of QALY gain, or *net⊿Q*) which includes any cost-savings (represented as equivalent health effects). Multiplying this quantity by the threshold generates a monetized value of the net-benefits of treatment that represent the maximum cost-effective incremental cost (price) that can be supported for the product. Note that since the value on the left-hand side of the equation is a QALY equivalent, the framework can be employed just on QALY differences or on a full net-equivalent QALY. This is important since in the case studies, we illustrate the framework only using published net-QALYs due to the restrictions imposed by working with information that is only available in the public domain.

4.2. Some notation

4.2.1. *Incremental benefits and value*

Let Q_A and Q_B be the net-equivalent QALYs attained from monotherapy with Therapy A and Therapy B, respectively, and $Q_{A,B}$ be the net-equivalent QALYs attained from Therapy A and Therapy B used in combination.

Let v_A be the monotherapy value of Therapy A and v_B be the monotherapy value of Therapy B for a given indication. Similarly, let $v_{A,B}$ be the value of the combination therapy composed of Therapy A and Therapy B for the same indication. The value of Therapy A, Therapy B, and the combination therapy are given by the following:

$$v_A = \lambda \cdot Q_A$$

$$v_B = \lambda \cdot Q_B$$

$$v_{A,B} = \lambda \cdot Q_{AB}$$

4.2.2. *Sub-additive versus synergistic benefits*

We say that a combination therapy is "additive" when the incremental benefit it generates equals the sum of the incremental benefits that each of its component therapies generate when used independently in the same indication, against the same comparator. That is, a combination therapy consisting of Therapy A and Therapy B is additive when the following relation holds:

$$Q_{AB} = Q_A + Q_B$$

A feature of combination therapies that makes value attribution challenging is that their efficacy is often less than additive in practice. In cases where the monotherapy effect of each component therapy is known, we often observe that combination therapies are strictly "sub-additive". A combination therapy is strictly sub-additive if it is more effective than each of the component therapies as monotherapies, but the incremental benefit generated by the combination is less than the sum of the incremental benefits of each component therapy when used alone. The following relation holds for strictly sub-additive combination therapies:

$$\max(Q_A, Q_B) < Q_{AB} < Q_A + Q_B$$

Value attribution is more challenging for strictly sub-additive combinations because the value of a strictly sub-additive combination therapy will be less than the sum of the independent values of its component therapies. This follows directly from the inequality shown above:

$$Q_{AB} < Q_A + Q_B$$

$$\lambda \cdot Q_{AB} < (\lambda \cdot Q_A) + (\lambda \cdot Q_B)$$

$$v_{A,B} < v_A + v_B$$

The last inequality implies that the value attributed to at least one of the component therapies will be less than its monotherapy value. It is this constraint that creates potential "winners" and "losers".

Combination therapies may also be synergistic, as described in section 3.1. The following relation will hold for synergistic combinations:

$$Q_{AB} > Q_A + Q_B$$

Although the manner in which value is attributed is still a concern for synergistic combinations, this scenario is less problematic since in this case $v_{A,B} > v_A + v_B$. This implies that the value that is attributed to each of the component therapies can be at least as great as their respective monotherapy values if not greater. In this scenario, there is potential for more than one "winner" and no "losers". We note that in cases where we have imperfect information about the independent benefits of component therapies, we cannot say with certainty whether a combination therapy is additive, strictly sub-additive, or synergistic.

4.3. The framework

Consider the combination therapy with component therapies A and B.[2] Let k_A be the proportion of the value of the combination therapy that is attributed to Therapy A, and let k_B be the proportion of the value that is attributed to Therapy B, where $k_A + k_B = 1$. Here we present a framework for selecting values for k_A and k_B that accounts for differences in the clinical effectiveness of therapies A and B as well as the balance of market power.

4.3.1. *Perfect information and balance of market power*

The simplest scenario is one where there is perfect information and balanced market power. In this scenario, we use what we know about the incremental benefits attained from monotherapy treatment with each of the component therapies to select k_A and k_B. Assume that the incremental benefit of monotherapy with each drug is strictly positive. We can then attribute value to each of the component therapies based on the amount each contributes to the sum of their independent benefits as follows:

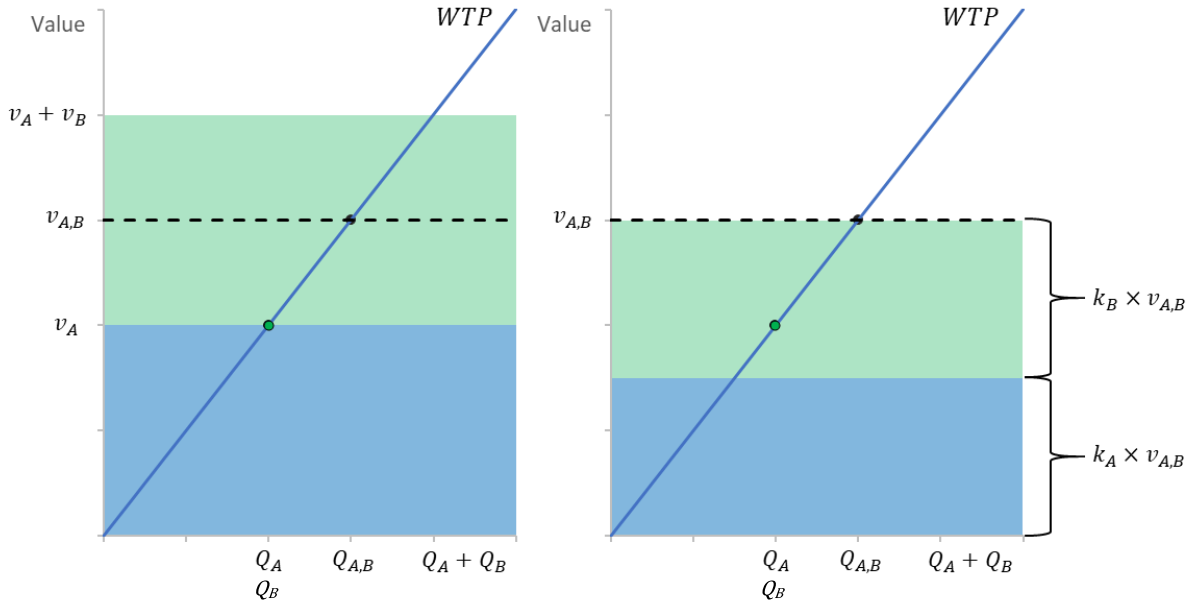
$$k_A = \frac{Q_A}{Q_A+Q_B} \text{ and } k_B = \frac{Q_B}{Q_A+Q_B} \qquad \textit{(Soln. 1)}$$

Figure 4.1 illustrates a case where the combination therapy consisting of Therapy A and Therapy B is strictly sub-additive. Since $Q_{A,B} < Q_A + Q_B$, it follows that $v_{A,B} < v_A + v_B$. The region shaded in blue represents the monotherapy value of Therapy A and the region shaded in green represents the monotherapy value of Therapy B. The sum of the monotherapy values of each drug is given by the height of the stacked blue and green regions. The maximum WTP for the incremental benefit generated by the combination therapy is given by the dashed line in Figure 4.1. The left panel of Figure 4.1 shows that the

[2] We present the framework using the simple case of a combination therapy consisting of two components. However, the framework can also be applied to combination therapies with more than two components. In the latter case, one or both of therapies A and B will be combination therapies consisting of more than one component.

sum of the monotherapy values of the component drugs exceeds the WTP for the incremental benefit generated by the combination therapy.

Figure 4.1. Perfect Information and Balanced Market Power Solution



The left panel of Figure 4.1 also shows that the monotherapy benefit of Therapy A equals that of Therapy B, i.e. $Q_A = Q_B$. This implies that $\frac{Q_A}{Q_A+Q_B} = \frac{Q_B}{Q_A+Q_B} = 0.5$. The solution for a scenario where there is perfect information and no imbalance of market power thus attributes an equal share of the value of the combination therapy to each component drug. This is shown in the right panel of Figure 4.1 above.

4.3.2. *Perfect information and imbalance of market power*

The solution presented above for the scenario where there is perfect information and no imbalance of market power accounts for observed differences in the clinical effectiveness of each of the component drugs. However, it does not account for differences in the timing of market entry and established market share. Suppose that Therapy A is the backbone therapy in the combination and was licensed and reimbursed on the market prior to the introduction of Therapy B. Since the manufacturer of Therapy A has the "first-mover advantage", it has less incentive to accept a share of the value of the combination that is less than the monotherapy value of Therapy A. The value attributed to Therapy A will equal its monotherapy value if k_A and k_B are chosen as follows:

$$k_A = \frac{Q_A}{Q_{A,B}} \text{ and } k_B = \frac{Q_{A,B} - Q_A}{Q_{A,B}}$$

This is true because $\frac{Q_A}{Q_{A,B}} \cdot v_{A,B} = v_A$. When the combination therapy is strictly sub-additive, the value attributed to Therapy A will be greater under this solution as compared to the solution for the perfect information scenario where there is no imbalance of market power.

However, if the combination therapy is synergistic, then the value attributed to Therapy A when $k_A = \frac{Q_A}{Q_{A,B}}$ would be less than the value it would be attributed if $k_A = \frac{Q_A}{Q_A + Q_B}$. Recall that the overall QALY gain is larger for synergistic combinations, since $Q_{A,B} > Q_A + Q_B$. This in turn implies that $v_{A,B} > v_A + v_B$ such that the value attributed to both component therapies could exceed their monotherapy value. Thus, although the value attributed to Therapy A equals its monotherapy value when $k_A = \frac{Q_A}{Q_{A,B}}$, in this case all of the value in excess of $v_A + v_B$ will be attributed to Therapy B. When there is an imbalance of market power, the manufacturer of the backbone therapy can select the solution that maximizes its share of the value. The solution in this scenario is thus the following:

$$k_A = max\left(\frac{Q_A}{Q_{A,B}}, \frac{Q_A}{Q_A + Q_B}\right) \text{ and } k_B = min\left(\frac{Q_{A,B} - Q_A}{Q_{A,B}}, \frac{Q_B}{Q_A + Q_B}\right), \qquad \textit{(Soln. 2)}$$

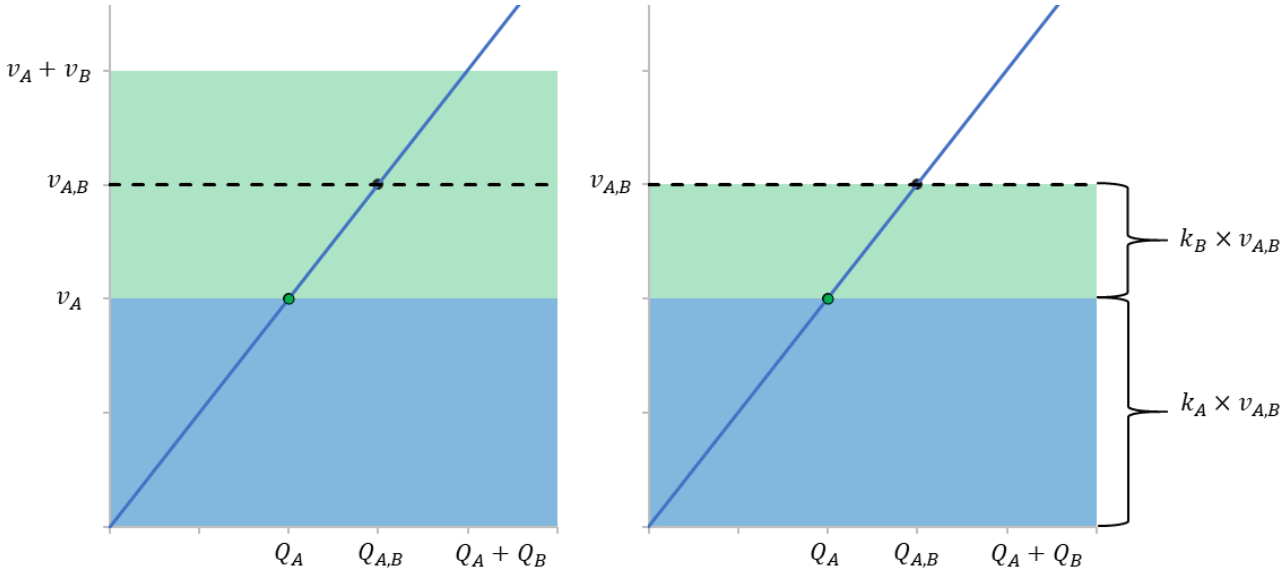
where *max* and *min* are functions that return the maximum and minimum values, respectively, of the parameters contained within the parentheses.

Here we demonstrate how the attribution of value between the component drugs changes when we have perfect information, but there is an imbalance of market power. Note that the following relations hold for strictly sub-additive combinations:

$$Q_{AB} < Q_A + Q_B \Rightarrow Q_A \cdot Q_{AB} < Q_A \cdot (Q_A + Q_B) \Rightarrow \frac{Q_A}{Q_A + Q_B} < \frac{Q_A}{Q_{A,B}}$$
$$\Rightarrow max\left(\frac{Q_A}{Q_{A,B}}, \frac{Q_A}{Q_A + Q_B}\right) = \frac{Q_A}{Q_{A,B}} \Rightarrow k_A = \frac{Q_A}{Q_{A,B}}$$

The above inequalities show that a greater share of the value of the combination is attributed to the backbone drug, Therapy A, when market power is imbalanced than when there was no imbalance of market power. Consequently, a lower share of the value of the combination is attributed to the add-on drug, Therapy B, when market power is imbalanced as compared to when it is balanced. This is shown below in the right panel of Figure 4.2. Note that the height of the blue rectangles shown in the left and right panels of Figure 4.2 are equal. This illustrates that the share of the value of the combination therapy that is attributed to Therapy A is equal to its value as a monotherapy.

Figure 4.2. Perfect Information and Imbalanced Market Power Solution



4.3.3. *Imperfect information and balance of market power*

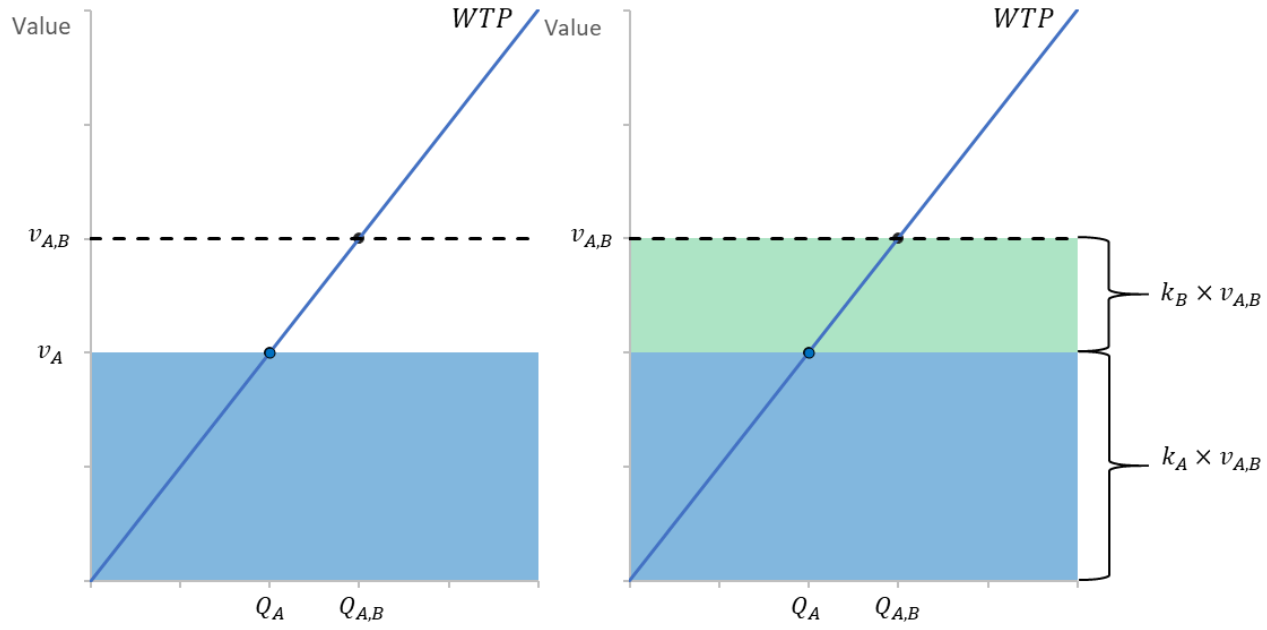
It is often the case that the independent benefit of the backbone therapy is known, but that the independent benefit of the add-on drug is unknown or cannot be measured (e.g. in the hypothetical case of a pharmacokinetic interaction). We would expect there to be an imbalance of market power in this case as well since the backbone therapy would have been available on the market prior to the introduction of the add-on drug. Furthermore, the backbone therapy can be used as a monotherapy, whereas the add-on therapy can only be used in combination with the backbone therapy for the indication in question. Yet even in a scenario where there is no imbalance of market power, an imbalance is created by the asymmetry in the available information.

Intuitively, our solution should resemble that presented for the perfect information scenario where there was an imbalance of market power. However, we cannot know whether the combination is strictly sub-additive or synergistic if we do not know the independent benefit of the new add-on drug. If we assume that the combination therapy is additive, then $\frac{Q_A}{Q_{A,B}} = \frac{Q_A}{Q_A+Q_B}$ and $\frac{Q_{A,B}-Q_A}{Q_{A,B}} = \frac{Q_B}{Q_A+Q_B}$. Thus, in a scenario where there is imperfect information, we assume that the combination is additive and select k_A and k_B as follows:

$$k_A = \frac{Q_A}{Q_{A,B}} \text{ and } k_B = \frac{Q_B}{Q_{A,B}} = \frac{Q_{A,B}-Q_A}{Q_{A,B}} \qquad \textit{(Soln. 3)}$$

Figure 4.3 illustrates the case of a combination therapy where the available information is imperfect, but market power is balanced. The independent value of the backbone drug, Therapy A, is known and represented by the rectangle shaded in blue in the left panel. The maximum WTP for the incremental benefit generated by the combination therapy is given by the dashed line in the figure. Since information is imperfect, we do not know the value of Therapy B as a monotherapy. Thus, we do not know whether the additive value of the component drugs falls above or below the WTP threshold. The solution presented above assumes that $Q_B = Q_{AB} - Q_A$ and attributes the entire value of the increment to the add-on drug. This is represented by the height of the green rectangle shown in the right panel of Figure 4.3. The value attributed to the backbone therapy then equals its monotherapy value as it did in the previous example.

Figure 4.3. Imperfect Information and Balanced Market Power Solution



4.3.4. *Imperfect information and imbalance of market power*

An imbalance of market power will typically be present in a scenario where there is imperfect information, and the component therapies are owned by different manufacturers, as discussed in section 4.3.3 above. This is the most encountered scenario in the "real world". We saw in section 4.3.2 that when there is an imbalance of market power, the value attributed to the backbone therapy will be greater than the value attributed to it when there is no imbalance of market power, all else equal. We would expect the same logic to hold in the present scenario where there is imperfect information and an imbalance of market

power. The manufacturer of the backbone therapy would favour a solution where $k_A > \frac{Q_A}{Q_{A,B}}$. The solution to the scenario where there is imperfect information and no imbalance of market power thus becomes a lower bound for the solution to the current problem. In this case, k_A and k_B will fall within the following ranges:

$$\frac{Q_A}{Q_{A,B}} \leq k_A < 1 \text{ and } 0 < k_B \leq \frac{Q_{A,B}-Q_A}{Q_{A,B}}, \text{ with } k_A + k_B = 1.$$

The "negotiable share" of the incremental value offered by the combination therapy consists of the set of possible values of k_A that fall between $\frac{Q_A}{Q_{A,B}}$ and 1 or some predefined subset of this interval. For example, the negotiable share may be predefined such that k_A and k_B must fall within the following intervals:

$$\begin{cases} \frac{Q_A}{Q_{A,B}} \leq k_A \leq (1+p) \cdot \frac{Q_A}{Q_{A,B}}, & \text{if } \frac{Q_A}{Q_{A,B}} < 0.50 \\ k_A = \frac{Q_A}{Q_{A,B}}, & \text{if } \frac{Q_A}{Q_{A,B}} \geq 0.50 \end{cases},$$

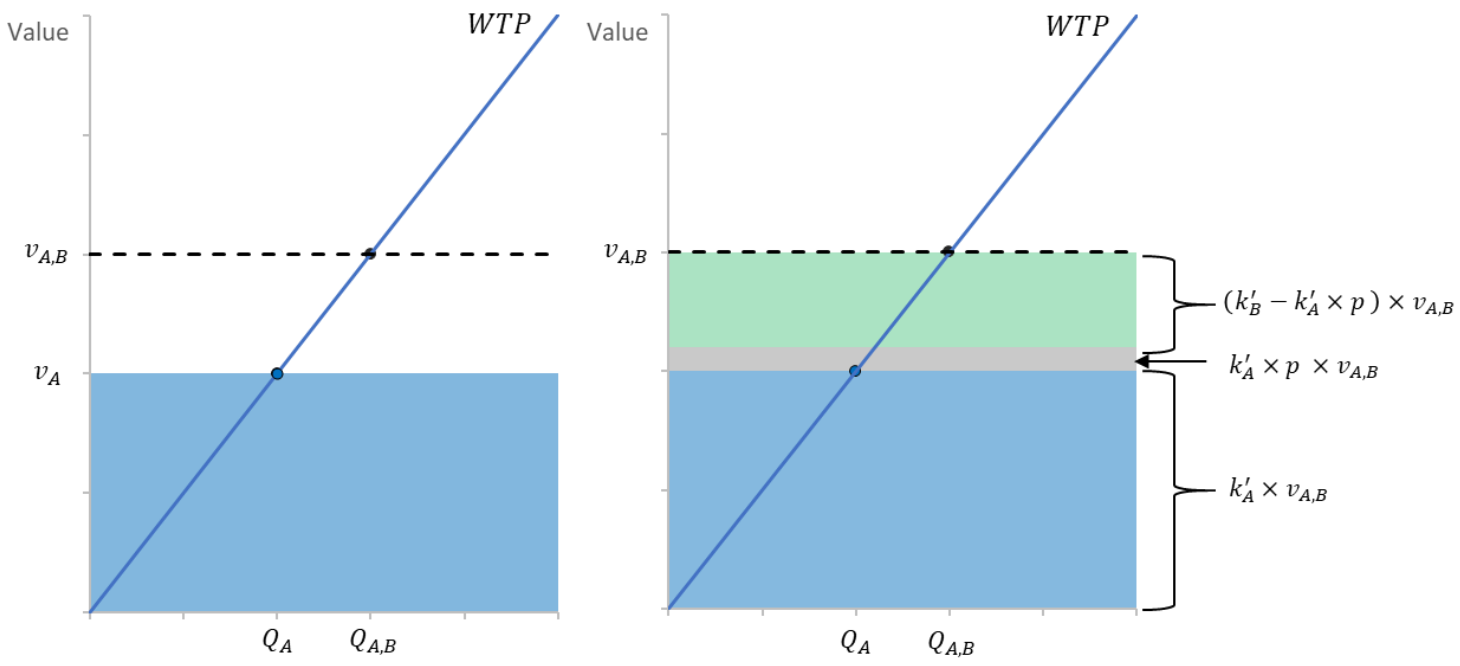
where p is a pre-specified value between 0 and 1. However, predefining the negotiable share in this way requires buy-in from both manufacturers; this is likely to be the main topic of negotiations among manufacturers should any dialogue or arbitration take place.

Figure 4.4 illustrates how the solution to a scenario where there is imperfect information and an imbalance of market power differs from that for the scenario where there is imperfect information, but market power is balanced. Let $k_A^{'} = \frac{Q_A}{Q_{A,B}}$ and $k_B^{'} = \frac{Q_{A,B}-Q_A}{Q_{A,B}}$ be the shares of the value of the combination that would be attributed to Therapy A and Therapy B, respectively, if there were no imbalance of market power. The grey rectangle in Figure 4.4 represents the negotiable share of the value of the combination therapy.[3] In this example, the size of the negotiable share equals some percentage p of the share that would be attributed to the backbone therapy if market power were balanced, where $0 \leq p < \frac{1}{k_A^{'}} - 1$. The shares of the value of the combination that are attributed to each of the component therapies will thus fall within the following intervals:

$$k_A^{'} \leq k_A \leq (1+p) \cdot k_A^{'} \text{ and } k_B^{'} - k_A^{'} \cdot p \leq k_B \leq k_B^{'}, \text{ with } k_A + k_B = 1 \qquad \textit{(Soln. 4)}$$

[3] Note that the size of the negotiable share was chosen arbitrarily in this example for illustrative purposes only.

Figure 4.4. Imperfect Information and Imbalanced Market Power Solution



4.3.5. *Summary of solutions*

The solutions to each of the four scenarios are summarized below in Table 4.3.1. Value Attribution Solutions by Scenario. We demonstrate the application of these scenarios in the case studies that follow in section 5.

Table 4.3.1. Value Attribution Solutions by Scenario

Scenario	$\boldsymbol{k_A}$	$\boldsymbol{k_B}$
Perfect Info, Balanced Power	$\frac{Q_A}{Q_A + Q_B}$	$\frac{Q_B}{Q_A + Q_B}$
Perfect Info, Unbalanced Power	$max\left(\frac{Q_A}{Q_{A,B}}, \frac{Q_A}{Q_A + Q_B}\right)$	$min\left(\frac{Q_{A,B} - Q_A}{Q_{A,B}}, \frac{Q_B}{Q_A + Q_B}\right)$
Imperfect Info, Balanced Power	$\frac{Q_A}{Q_{A,B}}$	$\frac{Q_{A,B} - Q_A}{Q_{A,B}}$

Imperfect Info, Unbalanced Power	$\frac{Q_A}{Q_{A,B}} \leq k_A < 1$	$0 < k_B \leq \frac{Q_{A,B} - Q_A}{Q_{A,B}}$

5. Case Studies

We demonstrate how the Attribution of Value Framework can be applied in practice through case studies of combination therapies that have been previously appraised by NICE. The case studies selected and detailed in this section were chosen solely for their illustrative value. To apply the Attribution of Value Framework, we require estimates for the clinical benefits corresponding to a combination therapy and each of its component therapies when these are known. Since we propose that the described methodology for value attribution can be incorporated into the current technology appraisal process, we obtain incremental QALY estimates from published NICE technology appraisals and related documents to demonstrate how the framework would be applied in practice. QALY estimates were selected for specific indications based on data availability. We use estimated incremental QALYs to link comparators across appraisals and estimate total QALYs. Throughout the case studies, we use the upper end of NICE's standard WTP of £30,000/QALY as the cost-effectiveness threshold, λ.

We note that there are larger issues related to the evaluation and selection of clinical evidence. One issue is that many therapies are used for more than one indication and reports suggest that at least 75% of cancer drugs will be marketed for multiple indications by 2020 [16, 17]. Trastuzumab, for example, is approved to treat HER2-positive metastatic gastric cancer as well as HER2-positive metastatic breast cancer [18, 19]. This poses a challenge for value attribution and pricing since the value of a drug and potential revenue is not constant across indications [2]. Furthermore, the value of a drug may also change over time as new indications are discovered through further research and development [3].

Even within a single indication, QALY estimates will vary depending upon factors such as the sources and strength of clinical evidence, data cut-off dates, and the structure and assumptions used in the underlying economic model. This raises questions related to the implementation of the framework. Which data to employ in the framework when there are competing estimates for the health benefits attained from treatment with a given therapy? How do we account for uncertainty stemming from immature data and changes in the strength of clinical evidence over time? Imbalances in the quality and quantity of evidence for established versus newly emerging drugs will also affect the process of value attribution. Although these questions and challenges must be addressed, they are not unlike those encountered during the process of conventional cost-effectiveness analyses and economic evaluation and are therefore not the focus of this framework.

One question that is central to the implementation of the framework is related to the classification of combination therapies within this framework. The framework assumes that the relative effectiveness of both therapies was estimated in direct or indirect comparisons (and QALY gain derived) using identical PICO elements i.e. in the same populations within the same indication, same comparators, under the

same conditions (dose, schedule of administration and positioning) and ideally QALY gains derived from the same clinical endpoints. Consequently, the "perfect information" scenario is an ideal scenario which is unfortunately rarely encountered in practice. What bar of clinical evidence is required to conclude that a given combination therapy satisfies the condition of "perfect information"? Early-phase trials often generate preliminary evidence of clinical efficacy. Is this evidence sufficient to conclude that a given therapy has value as a monotherapy? We suggest that early-phase safety and dose escalation trials provide insufficient evidence for establishing the monotherapy benefit of a given drug. Establishing whether the bar of evidence has been met is even more challenging when a component therapy has been studied in a phase III trial but was not administered following the same dosing schedule as when it is administered as part of the combination therapy. Component therapies may also have been studied in a different line of treatment or for a different indication than the combination is being appraised for. Do we assume that we lack perfect information when component therapies demonstrate efficacy in different lines of treatment? It is probable that the use of the framework will require some assumptions, scenario analyses, dialogue, cooperation and compromises which will allow its implementation. In particular, considering that the clinical evidence relevant to its implementation will have to be appropriately generated during the clinical development of either or both therapies, the implementation of the framework will benefit from early discussions between the companies involved and early dialogues with relevant HTA bodies.

We note that the combination therapies selected to illustrate the scenarios where there is no imbalance of market power are composed of component therapies that are produced by the same manufacturer. These therapies were selected for the case studies based on the available data. Arguably, cases where component therapies are produced by a single manufacturer pose the least challenge for value attribution. In these cases, all the value will be captured by the one manufacturer irrespective of how value is attributed to each of the component therapies. The manufacturer of a combination therapy consisting of n components can set each of $k_1, \ldots, k_n$ equal to any value between 0 and 1 so long as $k_1 + k_2 + \cdots + k_n = 1$. We do not attribute value specifically to generic drugs in the case studies for two reasons: (1) we do not believe the major issues that arise if combination therapies are found to be 'not cost-effective at zero price' are due to the generic component of combinations, and (2) manufacturers of patented component therapies can choose to manufacture generic components as well, thereby internalising the generic component of the combination. We present the case studies for each of the four scenarios in the sections that follow.

5.1. Perfect information and balanced market power: nivolumab with ipilimumab

Combination therapy with nivolumab and ipilimumab is indicated for the treatment of patients with unresectable or metastatic melanoma [20].[4] Nivolumab and ipilimumab are each approved as single-

[4] Nivolumab in combination with ipilimumab is also NICE recommended for patients in the UK with untreated advanced renal cell carcinoma and is currently under NICE appraisal for additional indications such as untreated unresectable malignant pleural mesothelioma and untreated advanced non-small-cell lung cancer [63, 64].

agent treatments for unresectable or metastatic melanoma as well [20, 21]. Since nivolumab and ipilimumab have been studied independently as well as in combination in phase III clinical trials for this indication, we have information about their independent clinical benefits [22–25]. This is thus a combination for which we have "perfect information" under the Attribution of Value Framework.

Ipilimumab was already available on the market and used in clinical practice for the treatment of advanced melanoma when both the NICE appraisals of single-agent nivolumab and nivolumab in combination with ipilimumab began in 2015 [26, 27].[5] Ipilimumab was the standard of care for treating the BRAF mutation-negative subtype of the disease, and was a treatment option for the BRAF mutation-positive subtype as well [28]. Since ipilimumab was registered first [20,21], we identify ipilimumab as the "backbone therapy" and nivolumab as the "add-on therapy". As ipilimumab had already been recommended by NICE as a monotherapy, at the time when the combination was being appraised, the manufacturer of ipilimumab would have had greater market power than the manufacturer of nivolumab. However, ipilimumab and nivolumab are both produced by the same manufacturer, so market power is balanced by default in this case.

When assessing the relative clinical benefits of component drugs, it is optimal to consider evidence from head-to-head clinical trials when available. Nivolumab and ipilimumab were compared alone and in combination as therapies for untreated metastatic melanoma in a randomized phase III clinical trial [24, 25, 29]. The clinical data suggest that the combination therapy is more effective than single-agent treatment with either of the component therapies (see Tables Table 5.1.1 through Table 5.1.3).

Survival estimates corresponding to nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab are shown below in Table 5.1.1. The combination therapy is associated with an estimated gain in median progression-free survival (PFS) of 4.6 months in comparison to nivolumab monotherapy and 8.6 months in comparison to ipilimumab monotherapy. Median overall survival (OS) in the combination therapy arm was not reached, but was greater than 60 months [28]. The combination is thus associated with an estimated gain in overall survival of more than 23.1 months in comparison to nivolumab monotherapy and more than 40.1 months in comparison to ipilimumab monotherapy. Furthermore, the data suggest that nivolumab monotherapy has greater clinical efficacy than ipilimumab monotherapy for the indication of advanced melanoma.

Table 5.1.1. Survival Estimates (in months)

Treatment	PFS	OS
Nivolumab with ipilimumab	11.5 (95% CI: 8.7-19.3)	Not reached (> 60)
Nivolumab	6.9 (95% CI: 5.1-10.2)	36.9 (95% CI: 28.2-58.7)

[5] NICE issued its final scope for an appraisal of single-agent nivolumab for treating advanced melanoma in July 2015. It issued its final scope for a separate appraisal of nivolumab in combination with ipilimumab for treating advanced melanoma just a few months later in November 2015.

Ipilimumab	2.9 (95% CI:2.8-3.2)	19.9 (95% CI: 16.8-24.6)

Source: [30]

Table 5.1.2. Hazard Ratio for Death

Treatment	Compared to Ipilimumab	Compared to Nivolumab
Nivolumab with ipilimumab	HR: 0.52 (95% CI: 0.42-0.64; P<0.001)	HR: 0.83 (95% CI: 0.67-1.03)
Nivolumab	HR: 0.63 (95% CI: 0.52-0.76; P<0.001)	–

Source: [29]

Table 5.1.3. Hazard Ratio for Disease Progression or Death

Treatment	Compared to Ipilimumab	Compared to Nivolumab
Nivolumab with ipilimumab	HR: 0.42 (95% CI: 0.35-0.51; P<0.001)	HR: 0.79 (95% CI: 0.64-0.96)
Nivolumab	HR: 0.53 (95% CI: 0.44-0.64; P<0.001)	–

Source: [29]

We demonstrate how the Attribution of Value Framework can be applied in this case using data that we obtained from publicly available documents from the NICE appraisals of nivolumab and nivolumab in combination with ipilimumab for treating advanced melanoma. To implement the solution to a perfect information scenario, we require incremental QALY estimates for the combination therapy as well as each of its component therapies. We use incremental QALY estimates for the BRAF mutation-negative subgroup of patients with advanced melanoma based on data availability [30. 31].[6] Dacarbazine is used as the common comparator in line with the appraisal of nivolumab monotherapy for this subgroup of patients. The incremental QALY estimates we use are shown below in Table 5.1.4. We obtain the monetized value of these incremental health benefits by multiplying each estimate by the willingness-to-pay for one additional QALY.

[6] These incremental QALY estimates were generated by the base case models the company submitted for technology appraisals of nivolumab monotherapy and nivolumab in combination with ipilimumab as treatments for advanced melanoma [30,31].

Table 5.1.4. Estimated QALYs for BRAF mutation-negative patients

Therapy	Total QALYs	ΔQALYs	Value
Dacarbazine	1.23	-------	-------
Ipilimumab	2.64	1.41	£42,300
Nivolumab	4.31	3.08	£92,400
Nivolumab + ipilimumab	4.83	3.60	£108,000

Substituting the incremental QALY estimates for the BRAF mutation-negative population into the framework gives the following:[7]

$$Q_{IPI} = 1.41$$
$$Q_{NIVO} = 3.08$$
$$Q_{NIVO,IPI} = 3.60$$
$$Q_{IPI} + Q_{NIVO} = 4.49$$

We observe that nivolumab with ipilimumab is a strictly sub-additive combination since

$$Q_{NIVO,IPI} < Q_{IPI} + Q_{NIVO}.$$

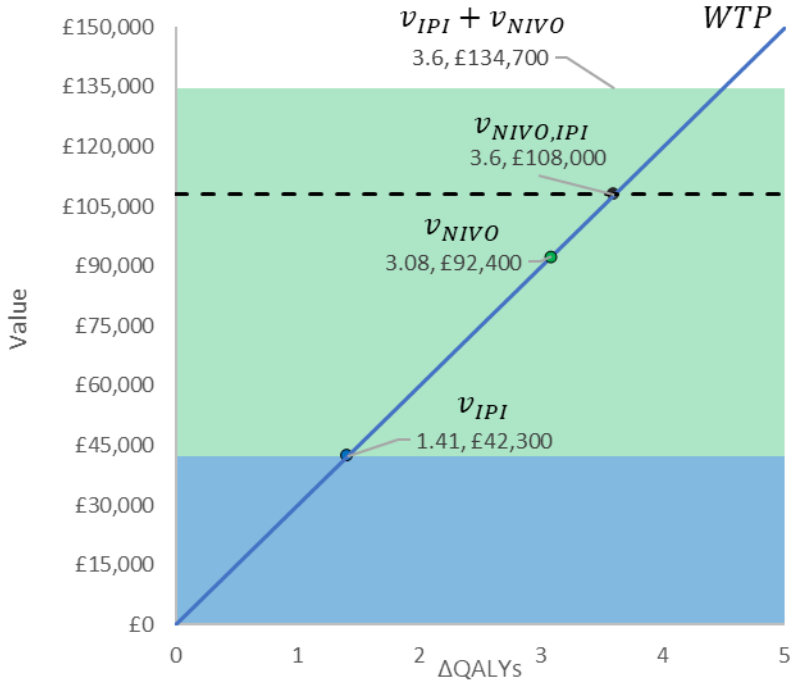
Let λ denote the WTP for an additional QALY. The value of each therapy is then given by $v_i = \lambda \times Q_i$, where i is an index that specifies the therapy. Setting WTP equal to £30,000 per QALY gained, the value of the combination therapy and each of its component drugs are as follows:

$$v_{IPI} = £42{,}300$$
$$v_{NIVO} = £92{,}400$$
$$v_{NIVO,IPI} = £108{,}000$$

Since the combination therapy is strictly sub-additive, the value of the combination is less than the sum of the independent values of its component therapies. That is, $v_{NIVO,IPI} < v_{IPI} + v_{NIVO}$. This is shown graphically below in Figure 5.1. We observe that the sum of the independent values exceeds the willingness-to-pay for the incremental benefits attained from treatment with the combination therapy.

[7] Abbreviations: IPI – ipilimumab; NIVO – nivolumab; NIVO,IPI – combination therapy with nivolumab and ipilimumab

Figure 5.1. Value and Willingness-to-Pay for Nivolumab with Ipilimumab



Abbreviations: IPI – ipilimumab, NIVO – nivolumab, NIVO,IPI – combination therapy with nivolumab and ipilimumab, WTP – willingness-to-pay (equals £30,000 per QALY gained).

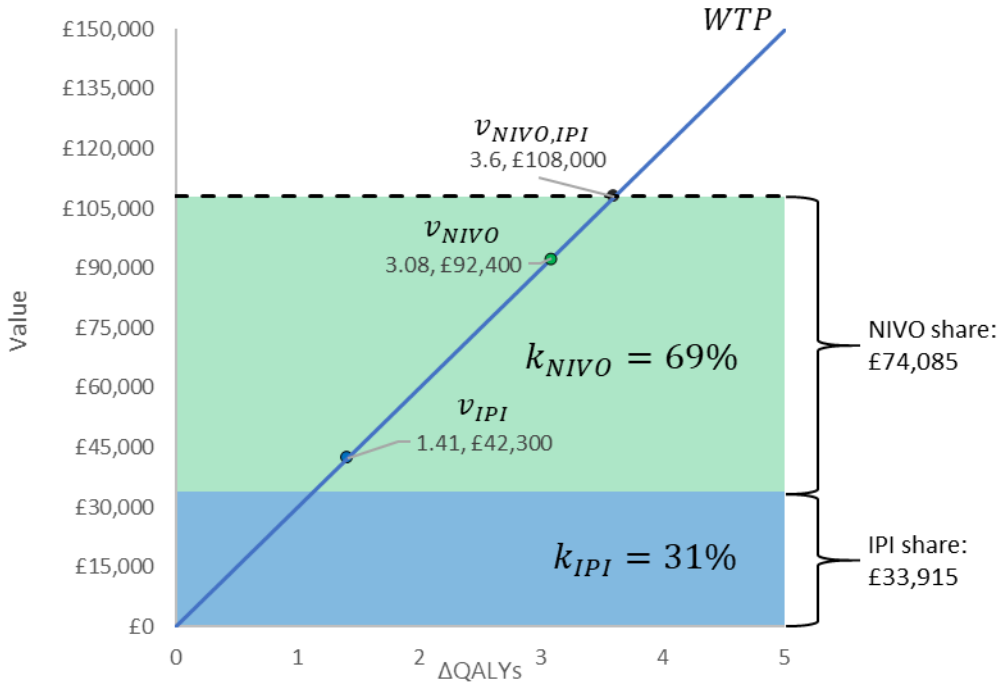
Since market power is balanced in the given example, we apply the value attribution solution corresponding to the perfect information and balanced market power scenario. Under this scenario, each of the component therapies receives a share of the value of the combination that is proportional to its share of the sum of their monotherapy benefits. In the current example, the value of the combination is attributed to each of the component therapies as follows:

$$k_{IPI} = \frac{Q_{IPI}}{Q_{NIVO} + Q_{IPI}} = \frac{1.41}{4.49} \approx 31\%$$

$$k_{NIVO} = \frac{Q_{NIVO}}{Q_{NIVO} + Q_{IPI}} = \frac{3.08}{4.49} \approx 69\%$$

The solution implies that 31% of the value of the combination is attributed to ipilimumab and 69% is attributed to nivolumab. Ipilimumab's contribution to the incremental benefit attained under the combination is valued at £33,915 and nivolumab's contribution is valued at £74,085. This is shown graphically below in Figure 5.2, where the shaded regions of the graph illustrate the share of the value of the combination that is attributed to each of the component therapies.

Figure 5.2. Case Study: Perfect Information and Balanced Market Power Solution



Abbreviations: IPI – ipilimumab, NIVO – nivolumab, NIVO,IPI – combination therapy with nivolumab and ipilimumab, WTP – willingness-to-pay (equals £30,000 per QALY gained).

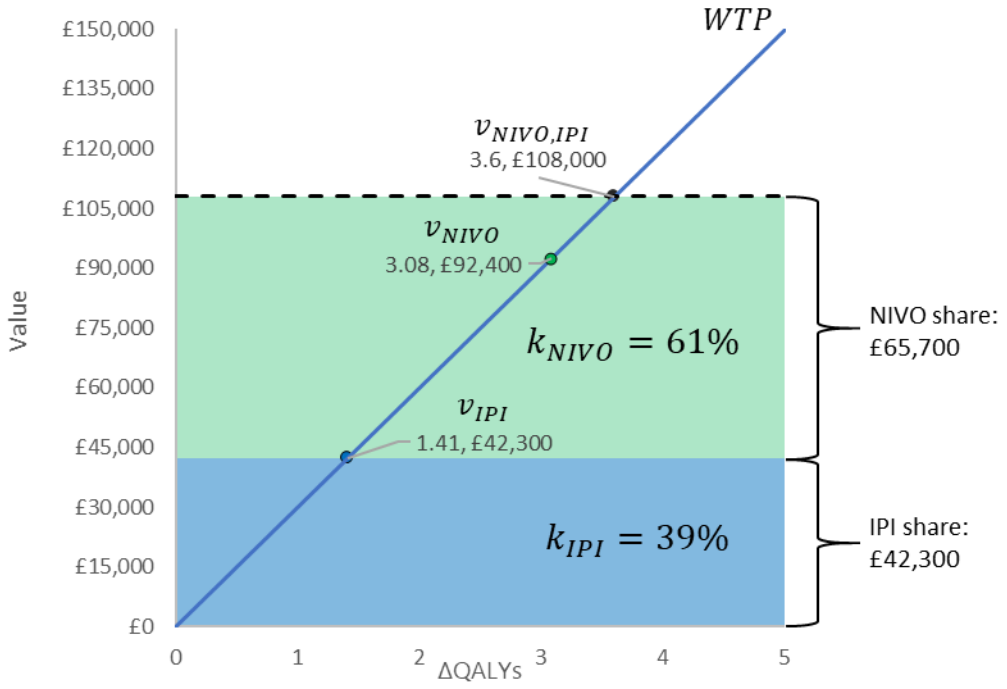
Now consider a hypothetical example where the incremental benefits of each of the therapies are the same as in the previous example, but market power is imbalanced. The value of the combination that is attributed to the backbone therapy equals its independent value, while the value of the incremental benefit obtained from treatment with the combination therapy is attributed to the add-on therapy as follows:

$$k_{IPI} = \frac{Q_{IPI}}{Q_{NIVO,IPI}} = \frac{1.41}{3.60} \approx 39\%$$

$$k_{NIVO} = \frac{Q_{NIVO} - Q_{IPI}}{Q_{NIVO,IPI}} = \frac{2.19}{3.60} \approx 61\%$$

The solution implies that 39% of the value of the combination is attributed to ipilimumab and 61% is attributed to nivolumab. Ipilimumab's contribution to the incremental benefit attained under the combination is valued at £42,300 and nivolumab's contribution is valued at £65,700. Under this scenario, the backbone therapy receives a higher share of the value of the combination than when market power is equal while the add-on therapy receives a lower share. This outcome is depicted below in Figure 5.3.

Figure 5.3. Illustrative Example: Perfect Information and Imbalanced Market Power Solution



Abbreviations: IPI – ipilimumab, NIVO – nivolumab, NIVO,IPI – combination therapy with nivolumab and ipilimumab, WTP – willingness-to-pay (equals £30,000 per QALY gained).

5.2. Perfect information and imbalanced market power: pembrolizumab with pemetrexed and platinum chemotherapy

Pembrolizumab with pemetrexed and platinum chemotherapy (carboplatin or cisplatin) is indicated as a first-line treatment for metastatic non-squamous non-small-cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations [32,33]. Pembrolizumab monotherapy is indicated as a first-line treatment for patients with metastatic NSCLC with programmed death-ligand 1 (PD-L1) tumour proportion score (TPS) ≥ 50% and no EGFR or ALK mutations [32,34]. Pemetrexed plus cisplatin is indicated as a first-line treatment for locally advanced or metastatic NSCLC other than predominantly squamous cell histology [35,36].

Pembrolizumab with pemetrexed and platinum chemotherapy (hereafter referred to as the pembrolizumab combination) satisfies the condition for perfect information for the subgroup of patients with metastatic non-squamous NSCLC without EGFR or ALK mutations with PD-L1 TPS ≥ 50% since the combination and each of its component therapies has been studied independently as treatments for this population in phase III clinical trials [37–40]. The pembrolizumab combination therapy also satisfies

the condition for imbalanced market power since pembrolizumab and pemetrexed have different manufacturers and pemetrexed-platinum was an established therapy for advanced non-squamous NSCLC when pembrolizumab was introduced into the market as a monotherapy. We do not consider the platinum-based chemotherapies as independent components since these drugs are available as generics that can be manufactured at low cost. We thus identify pemetrexed-platinum as the backbone therapy in the pembrolizumab combination and pembrolizumab as the add-on therapy.[8]

Survival and hazard ratio estimates based on the September 2018 data cut of the phase III clinical trial of the pembrolizumab combination are shown below in TablesTable 5.2.1 and Table 5.2.2, respectively. Although the trial included patients with untreated metastatic nonaqueous NSCLC without EGFR or ALK mutations regardless of their PD-L1 expression, these estimates are specific to the subgroup of patients with PD-L1 TPS ≥ 50%.

Table 5.2.1. Progression-free survival and Survival Estimates for Patients with PD-L1 TPS ≥ 50% (in months)

Treatment	PFS	OS
Pembrolizumab plus pemetrexed-platinum	11.1 (95% CI: 9.1, 14.4)	NR (95% CI: 20.4, NR)
Pemetrexed-platinum	4.8 (95% CI: 3.1, 6.2)	10.1 (95% CI: 7.5, NR)

Source: [38]

Table 5.2.2. Hazard Ratios for the Pembrolizumab Combination Compared to Pemetrexed-Platinum for Patients with PD-L1 TPS ≥ 50%

	Hazard Ratios
Hazard Ratio for Death	HR: 0.59 (95% CI: 0.39, 0.88)
Hazard Ratio for Disease Progression	HR: 0.36 (95% CI: 0.26, 0.51)

Source: [38]

The incremental benefits derived from treatment with the combination therapy and each of its component therapies are shown below in Table 5.2.3. Since pembrolizumab monotherapy is only

[8] We note that pembrolizumab monotherapy became the standard of care for treating patients with metastatic NSCLC with no EGFR or ALK mutations with PD-L1 TPS ≥ 50% after it received positive guidance from NICE in 2018 [33]. Given that, it is arguable that the manufacturer of pembrolizumab, who also sponsored the appraisal of the pembrolizumab combination, would have had greater market power than the manufacturer of pemetrexed at the time when the appraisal of the combination occurred. Furthermore, at the time when the pembrolizumab combination was being appraised, there was an expectation that generic versions of pemetrexed would soon be available [43]. As we discuss elsewhere, the challenges that make it difficult for novel combination therapies to demonstrate cost-effectiveness arise when component therapies are patented and cannot be produced at low cost. However, we assume that both component therapies are patented for the purpose of demonstrating the framework.

indicated for the subgroup of patients who are PD-L1-positive with TPS ≥ 50%, the estimated benefits we use to illustrate the framework are specific to this population.[9] The common comparator used is best supportive care.[10,11] The incremental benefit corresponding to treatment with pemetrexed-platinum was estimated using data obtained from a NICE appraisal of pemetrexed for the first-line treatment of NSCLC (TA181) and an appraisal of gemcitabine as a treatment for lung cancer (TA26) [38, 39].[12] The estimated incremental benefits corresponding to treatment with pembrolizumab monotherapy and the pembrolizumab combination are imputed using total QALY estimates reported in the NICE appraisal for pembrolizumab with pemetrexed and platinum chemotherapy (TA557) and the estimated incremental benefit for pemetrexed-platinum [43].

Table 5.2.3. Estimated QALYs for Patients with PD-L1 TPS ≥ 50%[13]

Therapy	Total QALYs	ΔQALYs	Value
Best supportive care	0.58	–	–
Pemetrexed-platinum	0.95	0.37	£11,100
Pembrolizumab	1.57	0.99	£29,700
Pembrolizumab with pemetrexed and platinum	2.35	1.77	£53,100

[9] There is a phase III clinical trial that compares pembrolizumab monotherapy to platinum-based chemotherapy as first-line treatments for patients with advanced NSCLC with a PD-L1 TPS ≥ 1% [65]. However, the technology appraisals for pembrolizumab monotherapy and the pembrolizumab combination were published before the completion of this study. We demonstrate the Attribution of Value Framework using data inputs for the subgroup of patients with advanced NSCLC who are PD-L1-positive with TPS ≥ 50% solely because of data availability.

[10] Other chemotherapies that are used as first-line treatments for advanced non-squamous NSCLC are gemcitabine, docetaxel, paclitaxel, or vinorelbine in combination with carboplatin or cisplatin [31]. These therapies were not selected as baseline comparators since they exhibit similar efficacy to pemetrexed-platinum. We use BSC as the common comparator, since it was used as such in the NICE appraisal of paclitaxel, docetaxel, gemcitabine and vinorelbine for lung cancer [42].

[11] We note that the estimated QALYs corresponding to BSC shown in Table 5.2.3 are for a general population of patients with lung cancer. The estimates are not specific to patients with PD-L1 TPS ≥ 50%.

[12] We estimate incremental QALYs for pemetrexed-platinum compared to BSC by linking the incremental QALYs for gemcitabine versus BSC reported in TA26 with the incremental QALYs for pemetrexed plus cisplatin versus gemcitabine plus cisplatin reported in TA181. The estimate for the incremental benefit corresponding to treatment with pemetrexed-platinum is therefore specific to the combination consisting of pemetrexed plus cisplatin, but we use it as a proxy for the combination consisting of pemetrexed plus carboplatin as well.

[13] The estimates shown in Table 5.2.3 are the discounted base-case results from the NICE appraisal of the pembrolizumab combination therapy [43]. The estimates are based on the results from the 2017 data cut of the phase III clinical trial of the pembrolizumab combination [37, 38].

Substituting the incremental QALY estimates into the framework gives the following:[14,15]

$$Q_{PEM,PLT} = 0.37$$
$$Q_{PBZ} = 0.99$$
$$Q_{PBZ,PEM,PLT} = 1.77$$
$$Q_{PEM,PLT} + Q_{PBZ} = 1.36$$

We observe that the estimated incremental QALYs shown in Table 5.2.3 above show that pembrolizumab with pemetrexed and platinum-based chemotherapy is a synergistic combination since:

$$Q_{PBZ,PEM,PLT} > Q_{PEM,PLT} + Q_{PBZ}.$$

Setting WTP equal to £30,000 per QALY gained, the value of the combination therapy and each of its component drugs are as follows:

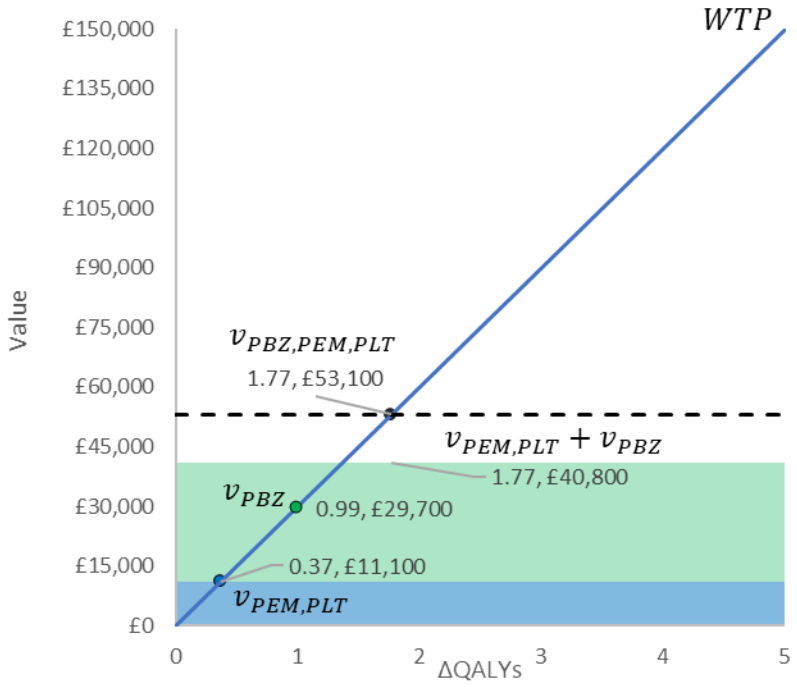
$$v_{PEM,PLT} = £11{,}100$$
$$v_{PBZ} = £29{,}700$$
$$v_{PBZ,PEM,PLT} = £53{,}100$$

Since the pembrolizumab combination therapy is synergistic, the value of the pembrolizumab combination is greater than the additive value of its component therapies. That is, $v_{PBZ,PEM,PLT} > v_{PEM,PLT} + v_{PBZ}$. This is shown graphically below in Figure 5.4. We observe that the WTP for the incremental benefit attained from treatment with the combination therapy exceeds the additive value of the component therapies.

[14] Abbreviations: PEM,PLT – pemetrexed with platinum chemotherapy; PBZ – pembrolizumab monotherapy; PBZ,PEM,PLT – combination therapy with pembrolizumab, pemetrexed and platinum chemotherapy

[15] The NICE appraisal for pembrolizumab monotherapy (TA531) suggests that the incremental benefit derived from treatment with single-agent pembrolizumab may be higher than the estimate reported in Table 5.2.3. The company's base case and updated base case models estimate that the incremental benefit derived from treatment with pembrolizumab monotherapy as compared to the standard of care (SOC) are 1.27 and 0.96, respectively, where SOC is a chemotherapy regimen (gemcitabine, paclitaxel, pemetrexed) combined with a platinum therapy (cisplatin or carboplatin). We use QALY estimates from the more recent appraisal of the pembrolizumab combination to demonstrate the Attribution of Value Framework.

Figure 5.4. Value and Willingness-to-Pay for Pembrolizumab with Pemetrexed and Platinum



Abbreviations: PEM,PLT – pemetrexed-platinum, PBZ – pembrolizumab, PBZ,PEM,PLT – combination therapy with pembrolizumab and pemetrexed-platinum, WTP – willingness-to-pay (equals £30,000 per QALY gained).

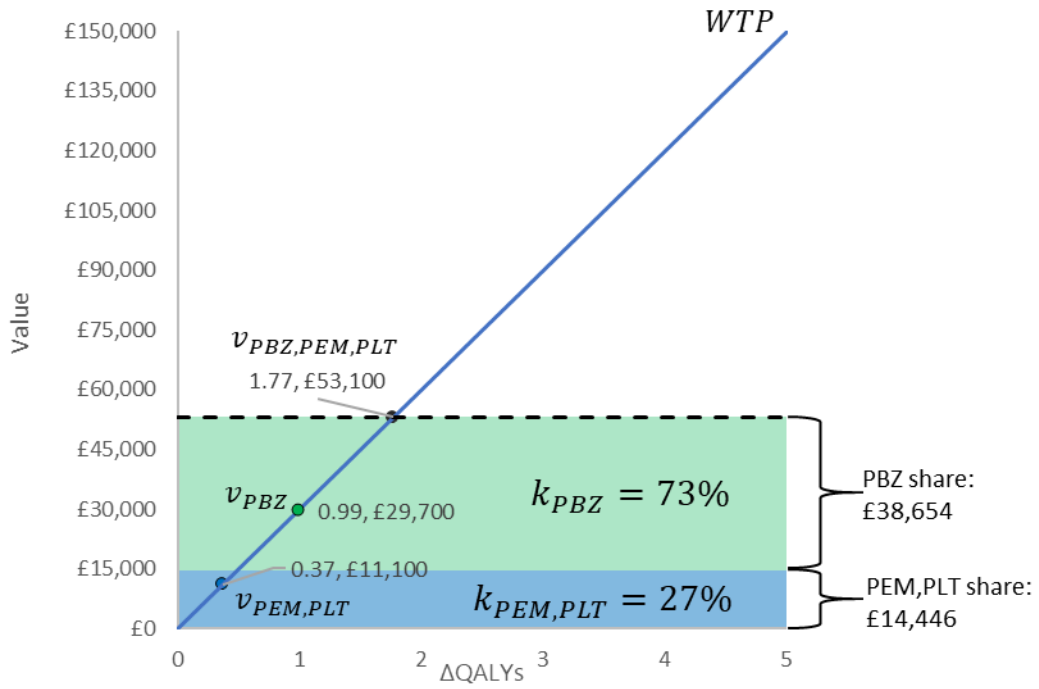
When market power is imbalanced, the manufacturer with more power will seek to capture a greater share of the value of the combination or be less inclined to cede value than it would if market power were balanced. Under this scenario, the manufacturer of the backbone therapy receives a share of the value of the novel combination that equals the ratio of its independent benefit to the benefit of the combination if the resulting share is greater than the share it would receive under the corresponding balanced market power scenario. The value of the pembrolizumab combination is attributed to each of the component therapies as follows:

$$k_{PEM,PLT} = \max\left(\frac{Q_{PEM,PLT}}{Q_{PBZ,PEM,PLT}}, \frac{Q_{PEM,PLT}}{Q_{PEM,PLT} + Q_{PBZ}}\right) = \max\left(\frac{0.37}{1.77}, \frac{0.37}{1.36}\right) \approx \max\left(0.21, 0.27\right) \approx 27\%$$

$$k_{PBZ} = \min\left(\frac{Q_{PBZ,PEM,PLT} - Q_{PEM,PLT}}{Q_{PBZ,PEM,PLT}}, \frac{Q_{PBZ}}{Q_{PEM,PLT} + Q_{PBZ}}\right) = \min\left(\frac{1.40}{1.77}, \frac{0.99}{1.36}\right) \approx \min(0.79, 0.73) \approx 73\%$$

The solution implies that 27% of the value of the combination is attributed to the backbone, pemetrexed with platinum chemotherapy and 73% is attributed to the add-on, pembrolizumab. In the combination, the contribution of pemetrexed-platinum to the incremental benefit is valued at £14,446 and the contribution of pembrolizumab is valued at £38,654. This is shown below in Figure 5.5.

Figure 5.5. Case Study: Perfect Information and Imbalanced Market Power Solution

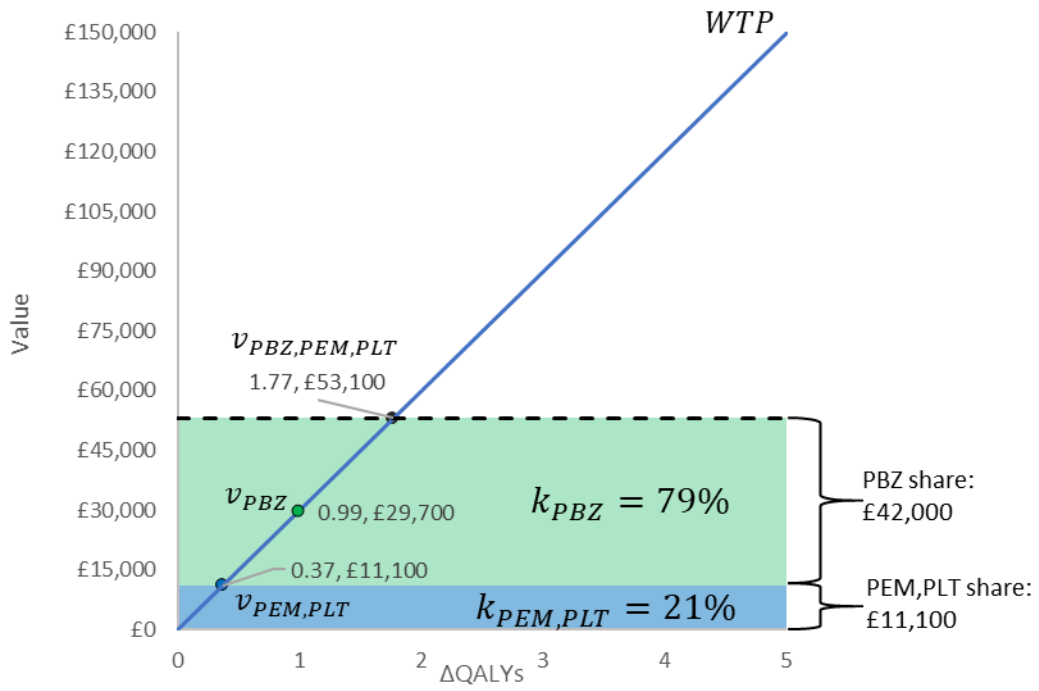


Abbreviations: PEM,PLT – pemetrexed-platinum, PBZ – pembrolizumab, PBZ,PEM,PLT – combination therapy with pembrolizumab and pemetrexed-platinum, WTP – willingness-to-pay (equals £30,000 per QALY gained).

Note that in this example, the resulting attribution of value when market power is imbalanced is the same that would result if market power were balanced. This will be true for all combinations that are additive or synergistic. If the share of the value attributed to pemetrexed-platinum were given by $k_{PEM,PLT} = \frac{Q_{PEM,PLT}}{Q_{PBZ,PEM,PLT}} \approx 21\%$ instead, then the backbone therapy would receive a share of the value of the pembrolizumab combination such that the value of this share and the independent value of the backbone therapy are equal. However, the backbone therapy would then fail to capture any of the synergistic gains where the value of the pembrolizumab combination exceeds the additive value of its component therapies. This is shown below in Figure 5.6. If the combination therapy were strictly sub-additive, however, then a greater share of the value of the combination would be attributed to the backbone therapy if $k_{PEM,PLT} = \frac{Q_{PEM,PLT}}{Q_{PBZ,PEM,PLT}}$ as compared to when $k_{PEM,PLT} = \frac{Q_{PEM,PLT}}{Q_{PEM,PLT}+Q_{PBZ}}$. In general,

the resulting attribution of value for a strictly sub-additive combination therapy for which perfect information exists will differ depending upon whether market power is balanced or imbalanced, even when all other factors are held constant.

Figure 5.6. Illustrative Example: Attribution of Value if $k_{PEM,PLT} = \frac{Q_{PEM,PLT}}{Q_{PBZ,PEM,PLT}}$



Abbreviations: PEM,PLT – pemetrexed-platinum, PBZ – pembrolizumab, PBZ,PEM,PLT – combination therapy with pembrolizumab and pemetrexed-platinum, WTP – willingness-to-pay (equals £30,000 per QALY gained).

5.3. Imperfect information and balanced market power: pertuzumab with trastuzumab and docetaxel

Pertuzumab with trastuzumab and docetaxel is indicated for the treatment of patients with HER2-positive metastatic or locally recurrent unresectable breast cancer (HER2+ mBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease [32, 44]. This combination therapy holds significance as its appraisal motivated the original work culminating in the 2014 NICE Decision Support Unit (DSU) report that illustrates how health technologies can fail to be cost-effective even at 'zero price' [1, 12]. This work defined what is now well-recognized as a key challenge to the economic evaluation of combination therapies in oncology—that clinically effective therapies can fail to be cost-effective, even at zero cost of the add-on therapy, because gains in progression-free survival

extend the duration of treatment with a patented and thus costly backbone therapy. As the current work on developing an Attribution of Value Framework for combination therapies builds upon the earlier work conducted by the DSU, we present a case study where we apply the framework to the combination therapy consisting of pertuzumab with trastuzumab and docetaxel (hereafter referred to as the "pertuzumab combination").

Trastuzumab plus a taxane was a widely used first-line treatment for HER2+ mBC prior to the introduction of pertuzumab [45].[16] Since trastuzumab had an established market share at the time when pertuzumab was a new market entrant, we identify trastuzumab as the backbone therapy and pertuzumab as the add-on therapy in the combination. We do not consider docetaxel as an independent component since it is a generic chemotherapy. Since pertuzumab and trastuzumab have the same manufacturer, market power is balanced by default, regardless of order of market entry. However, pertuzumab is only indicated for use in combination with trastuzumab as it was solely evaluated as a component of the combination in Phase III trials. [46-48].[17] We thus have imperfect information about its independent clinical benefit.

Treatment with the pertuzumab combination was compared to treatment with trastuzumab and docetaxel in a phase III clinical trial [10, 49, 50]. Survival estimates and hazard ratios derived from an analysis of data collected up until the 2014 cut-off are shown below in Tables Table 5.3.1 and Table 5.3.2. We observe from Table 5.3.1 that median progression-free survival was approximately 6.3 months longer in the group of patients treated with the pertuzumab combination as compared to the group treated with the backbone therapy alone. Similarly, median overall survival was approximately 15.7 months longer in the group of patients treated with the pertuzumab combination.

Table 5.3.1. Progression-free survival and Survival Estimates (in months)

Treatment	PFS	OS
Pertuzumab with trastuzumab and docetaxel	18.7 (95% CI: 16.6-21.6)	56.5 (95% CI: 49.3-NR)
Trastuzumab and docetaxel	12.4 (95% CI: 10.4-13.5)	40.8 (95% CI: 35.8-48.3)

Source: [46, 49]; NR – not reached

[16] We note that pertuzumab in combination with trastuzumab and docetaxel became available through the Cancer Drugs Fund (CDF) in 2013. It had replaced trastuzumab plus docetaxel as the standard of care prior to receiving positive guidance from NICE in 2018 [44].

[17] One phase II clinical study was identified where pertuzumab was evaluated as a single-agent treatment for patients with HER2+ mBC [66]. However, pertuzumab was not evaluated as a first-line treatment in this study, as 86% of the study population had received prior treatment for metastatic disease (ibid.) thus the study does not qualify for providing suitable monotherapy data.

Table 5.3.2. Hazard Ratios for the Pertuzumab Combination Compared to Trastuzumab plus Docetaxel

	Hazard Ratios
Hazard Ratio for Death	HR: 0.68 (95% CI: 0.56-0.84); P<0.001
Hazard Ratio for Disease Progression	HR: 0.68 (95% CI: 0.58-0.80); P<0.001

Source: [49]

The survival gains resulting from treatment with the pertuzumab combination were described as being unprecedented for the indicated population [50]. Yet the NICE appraisal committee initially found that there was no price at which pertuzumab could be cost-effective at the accepted WTP threshold of £30,000 per QALY gained. It was this outcome—that existing methods of assessing cost-effectiveness would prevent patient access to a ground-breaking therapy—that prompted NICE to pause its appraisal of the pertuzumab combination and commission the DSU report that has been described elsewhere in this paper. In its report, the DSU demonstrated that although the incremental change in QALYs resulting from treatment with the pertuzumab combination was substantial, the incremental change in costs stemming solely from the increased duration of treatment with trastuzumab and docetaxel meant that the pertuzumab combination could not be cost-effective even if the price of pertuzumab were equal to zero.

For the pertuzumab combination to be considered cost-effective, the price of trastuzumab would have to be reduced. We show how the Attribution of Value Framework could be applied in this case to determine how the value of the combination should be attributed to each of its components. Table 5.3.3 presents data obtained from publicly available documents from the NICE single technology appraisal of the pertuzumab combination as a first-line treatment for HER2-positive metastatic or locally unresectable breast cancer. The QALY estimates shown in Table 5.3.3 are based on the primary and interim analyses of the 2011 and 2012 cuts of the clinical trial data [10, 44]. These are the deterministic estimates generated by the original base case model that the company submitted to NICE for the appraisal that was paused in 2013.[18]

[18] The revised economic model the company submitted to NICE for the final 2018 appraisal was based on an analysis of the 2014 data cut [51]. We use the original base case estimates due to data availability.

Table 5.3.3. Estimated QALYs and Total Costs for the Pertuzumab Combination and Backbone Therapy

Therapy	Total QALYs	ΔQALYs	Value
Docetaxel	1.81	-------	-------
Trastuzumab plus docetaxel	2.60	0.79	£23,700
Pertuzumab with trastuzumab and docetaxel	3.50	1.69	£50,700

Source: [51]

We use the QALY estimates shown in Table 5.3.3 to demonstrate how value would be attributed to each of the component therapies in this scenario where market power is balanced but information is imperfect. Substituting the QALYs produced by the company's base case model into the framework gives the following:

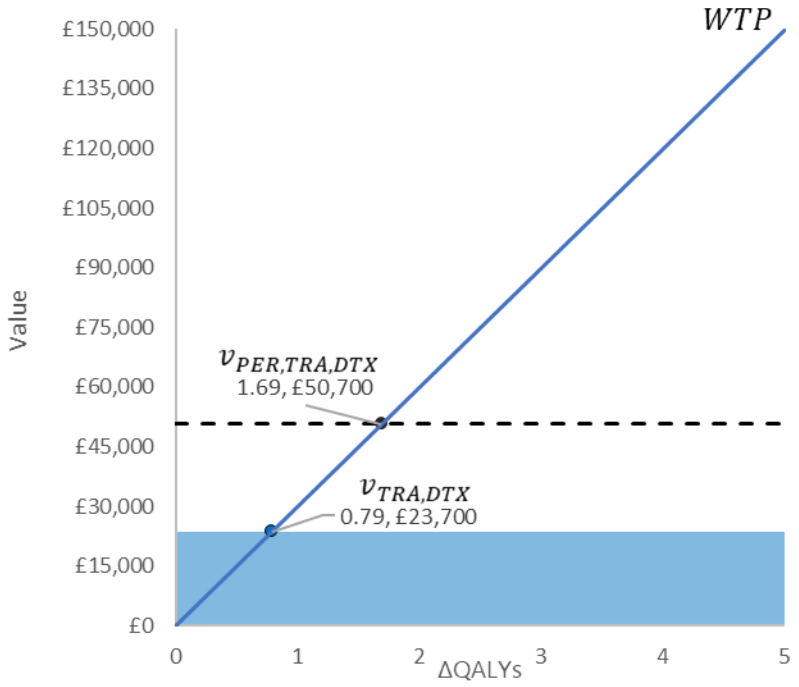
$$Q_{TRA,DTX} = 0.79$$
$$Q_{PER} = ?$$
$$Q_{PER,TRA,DTX} = 1.69$$
$$Q_{TRA,DTX} + Q_{PER} = ?$$

Setting WTP equal to £30,000 per QALY gained, the value of the combination therapy and each of its component therapies are as follows:

$$v_{TRA,DTX} = \text{£}23{,}700$$
$$v_{PER} = \lambda \times Q_{PER} = ?$$
$$v_{PER,TRA,DTX} = \text{£}50{,}700$$

Since we do not have monotherapy data for pertuzumab in this setting and we do not know Q_{PER}, we do not know the independent value of the add-on therapy, v_{PER}. We also do not know whether the pertuzumab combination is strictly sub-additive, additive, or synergistic. This fact is illustrated below in Figure 5.7.

Figure 5.7. Value and Willingness-to-Pay for Pertuzumab with Trastuzumab and Docetaxel



Abbreviations: TRA,DTX – trastuzumab and docetaxel, PER,TRA,DTX – combination therapy with pertuzumab plus trastuzumab and docetaxel, WTP – willingness-to-pay (equals £30,000 per QALY gained).

Given this uncertainty, we assume that the combination is additive such that the following relation holds:

$$Q_{PER,TRA,DTX} = Q_{TRA,DTX} + Q_{PER} \Rightarrow Q_{PER} = Q_{PER,TRA,DTX} - Q_{TRA,DTX}$$

In the case of the current example, this implies that

$$1.69 = 0.79 + Q_{PER} \Rightarrow Q_{PER} = 0.90$$

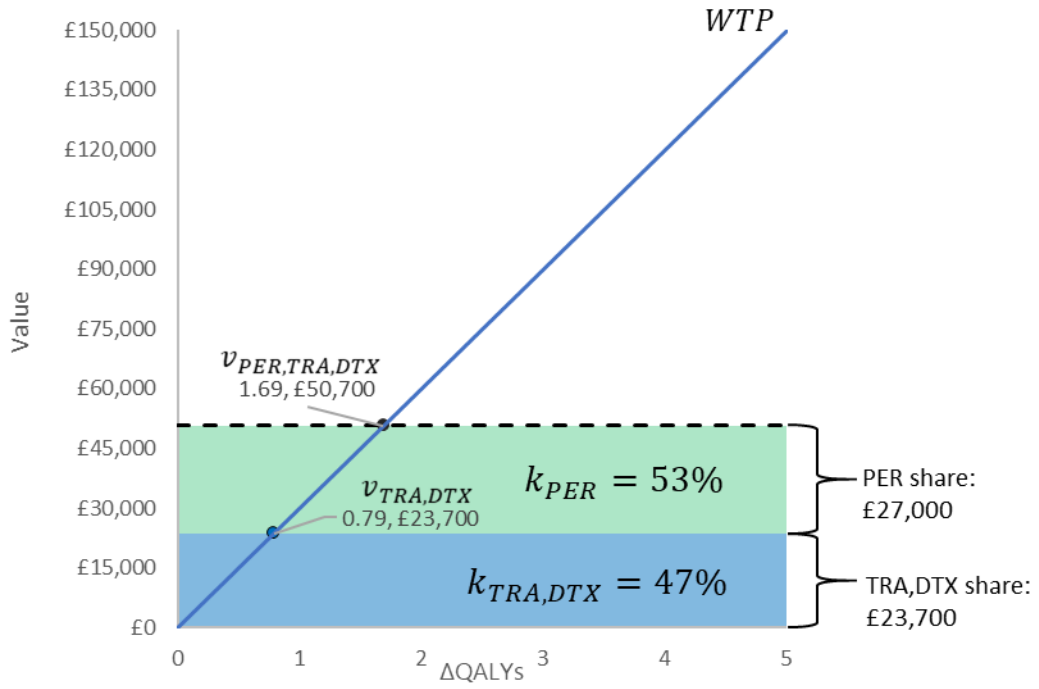
Using the resulting value for Q_{PER}, we can solve the given value attribution problem as if we had perfect information and market power were equal. The share of the value of the pertuzumab combination that is attributed to each of the component therapies is given by the following:

$$k_{TRA,DTX} = \frac{Q_{TRA,DTX}}{Q_{TRA,DTX} + Q_{PER}} = \frac{Q_{TRA,DTX}}{Q_{PER,TRA,DTX}} = \frac{0.79}{1.69} \approx 47\%$$

$$k_{PER} = \frac{Q_{PER}}{Q_{TRA,DTX} + Q_{PER}} = \frac{Q_{PER,TRA,DTX} - Q_{TRA,DTX}}{Q_{PER,TRA,DTX}} = \frac{0.90}{1.69} \approx 53\%$$

The resulting values for $k_{TRA,DTX}$ and k_{PER} imply that £23,700 of the value of the pertuzumab combination is attributed to trastuzumab plus docetaxel, and £27,000 is attributed to pertuzumab. This is shown below in Figure 5.8. The value attributed to the backbone therapy equals its monotherapy value since we assumed that the combination is additive. The remaining value of the incremental benefit attained from treatment with the pertuzumab combination is fully attributed to pertuzumab.

Figure 5.8. Case Study: Imperfect Information and Balanced Market Power Solution



Abbreviations: TRA,DTX – trastuzumab and docetaxel, PER,TRA,DTX – combination therapy with pertuzumab plus trastuzumab and docetaxel, WTP – willingness-to-pay (equals £30,000 per QALY gained).

5.4. Imperfect information and imbalanced market power: carfilzomib with lenalidomide and dexamethasone

Carfilzomib with lenalidomide and dexamethasone is indicated for the treatment of patients with multiple myeloma (MM) who have received one or more prior lines of therapy [52]. At the time when the carfilzomib combination was being appraised by NICE, lenalidomide with dexamethasone (lenalidomide-dexamethasone) had been appraised and recommended for the treatment of patients with MM who have received two or more prior lines of therapy [53]. We therefore restrict our analysis to the population of patients with MM who have received two or more prior lines of therapy and no prior treatment with lenalidomide.

Lenalidomide-dexamethasone has been evaluated as a treatment for relapsed or refractory (RR) MM in phase III clinical trials [54, 55], so we have information about its independent benefit for the given indication. Although single-agent carfilzomib has been evaluated as a treatment for RRMM, these were small sample studies that followed a different dosing schedule than the carfilzomib combination under consideration or included patients who received prior treatment with lenalidomide [56-60]. We thus do not have information about the independent benefit attained from treatment with single-agent carfilzomib for the given indication. Since carfilzomib and lenalidomide have different manufacturers, and lenalidomide-dexamethasone was an established therapy for RRMM when carfilzomib entered the market [52], the carfilzomib combination reflects a scenario where there is imperfect information and an imbalance of market power. We identify lenalidomide-dexamethasone as the backbone therapy in this case since it was registered first, and carfilzomib as the add-on therapy. Because it is an inexpensive medicine, we consider that dexamethasone is a negligible component of the combination therapy which could therefore be disregarded.

Survival estimates from the phase III trial that compared treatment with the carfilzomib combination to treatment with lenalidomide-dexamethasone are shown below in Table 5.4.1. The corresponding hazard ratio estimates are shown in Table 5.4.2. These estimates are based on trial data collected until the final April 2017 cut-off.[19] We note that these results were for the entire sample of patients included in the study and are not specific to patients who received two or more prior lines of therapy.

Table 5.4.1. Progression-free survival and Survival Estimates (in months)

Treatment	PFS	OS
Carfilzomib with lenalidomide-dexamethasone	26.1 (95% CI: 23.2-30.3)	48.3 (95% CI: 42.4-52.8)
Lenalidomide-dexamethasone	16.6 (95% CI: 14.5-19.4)	40.4 (95% CI: 33.6-44.4)

Source: [55]

Table 5.4.2. Hazard Ratios for the Carfilzomib Combination Compared to Lenalidomide-Dexamethasone

	Hazard Ratios
Hazard Ratio for Death	HR: 0.79 (95% CI: 0.67-0.95); P=.0045
Hazard Ratio for Disease Progression	HR: 0.66 (95% CI: 0.55-0.78); P<.001

Source: [55]

[19] The QALY estimates reported in Table 5.4.3 are based on the interim analysis of trial data collected until the June 2014 cut-off [54, 61].

As described in the NICE submission, the carfilzomib combination is an example of a scenario where an add-on drug combined with an existing backbone therapy is not cost-effective even when the price of the add-on equals zero [61], Patients are treated with the carfilzomib combination until disease-progression or unacceptable toxicity occurs. Since progression-free survival was roughly 9.5 months longer in the combination therapy arm compared to the backbone arm of the phase III trial, the duration of treatment with lenalidomide was longer on average in the group of patients treated with the carfilzomib combination. This shows that, even without accounting for the cost of carfilzomib, treatment costs are higher for carfilzomib combination therapy due to the additional lenalidomide. Furthermore, in this case the backbone therapy met the end-of-life criteria during its own appraisal and was priced according to the higher WTP threshold, whereas the combination therapy did not meet the criteria because the life-expectancy of the patients eligible for the combination therapy was now longer than 24 months. These factors made it challenging for the carfilzomib combination to be considered cost-effective.

Table 5.4.3 contains QALY estimates that were obtained from publicly available documents from the 2017 NICE appraisal for the carfilzomib combination and the 2009 appraisal for lenalidomide-dexamethasone for previously treated multiple myeloma [57, 58]. These estimates are specific to the subgroup of patients who received two prior therapies and no prior lenalidomide. This finding again highlights how combination therapies often fail to be cost-effective because gains in progression-free survival increase the duration of treatment with the backbone therapy, which generates additional costs [1, 12, 61]. This is further complicated due to the imbalance of market power as the combination components are manufactured by different companies.

Table 5.4.3. QALYs and Total Costs for Patients who Received Two or More Prior lines of Therapy[20]

Therapy	Total QALYs	ΔQALYs	Value
Dexamethasone	0.87	-------	-------
Lenalidomide-dexamethasone	3.33	2.46	£73,800
Carfilzomib with lenalidomide-dexamethasone	4.32	3.45	£103,500

Source: [61, 62]

Substituting the incremental QALY estimates from Table 5.4.3 into the Attribution of Value Framework gives the following:[21]

[20] These estimates reflect the results generated by the companies' original base case models.
[21] Abbreviations: LEN,DEX – lenalidomide-dexamethasone; CFZ – carfilzomib; CFZ,LEN,DEX – combination therapy with carfilzomib and lenalidomide-dexamethasone /

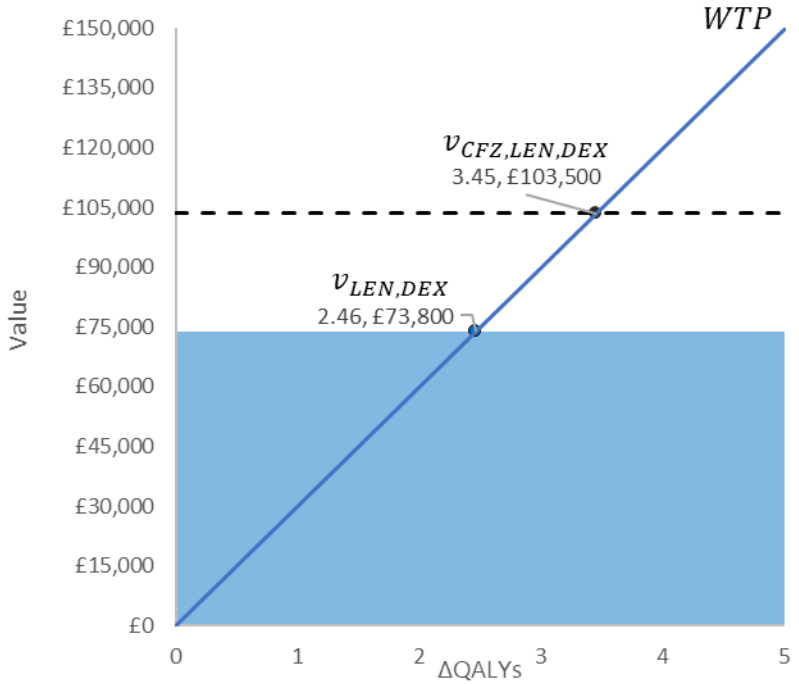
$$Q_{LEN,DEX} = 2.46$$
$$Q_{CFZ} = ?$$
$$Q_{CFZ,LEN,DEX} = 3.45$$
$$Q_{LEN,DEX} + Q_{CFZ} = ?$$

Setting WTP equal to £30,000 per QALY gained, the value of the combination therapy and each of its component drugs are as follows:

$$v_{LEN,DEX} = £73{,}800$$
$$v_{CFZ} = ?$$
$$v_{CFZ,LEN,DEX} = £103{,}500$$

Since we do not have appropriate monotherapy data on carfilzomib in this setting, we do not know Q_{CFZ}, and so we do not know the independent value of the add-on therapy, v_{CFZ}. We also do not know whether the carfilzomib combination is strictly sub-additive, additive, or synergistic. This is illustrated below in Figure 5.9.

Figure 5.9. Value and Willingness-to-Pay for Carfilzomib with Lenalidomide and Dexamethasone



Abbreviations: LEN,DEX – lenalidomide and dexamethasone, CFZ,LEN,DEX – combination therapy with carfilzomib plus lenalidomide and dexamethasone, WTP – willingness-to-pay (equals £30,000 per QALY gained).

If we assume that the combination is additive, then the following relation holds:

$$Q_{CFZ,LEN,DEX} = Q_{LEN,DEX} + Q_{CFZ} \Rightarrow Q_{CFZ} = Q_{CFZ,LEN,DEX} - Q_{LEN,DEX}$$

In the case of the current example, this implies that

$$3.45 = 2.46 + Q_{CFZ} \Rightarrow Q_{CFZ} = 0.99$$

Suppose that the negotiable share of the combination therapy is predefined such that[22]:

$$\begin{cases} \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} \leq k_{LEN,DEX} \leq (1+p) \cdot \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}}, & \text{if } \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} < 0.50, \quad where\ p = 0.10 \\ k_{LEN,DEX} = \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}}, & \text{if } \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} \geq 0.50 \end{cases}$$

Since $\frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} \approx 0.71 > .050$, we obtain the following solution to the value attribution problem:

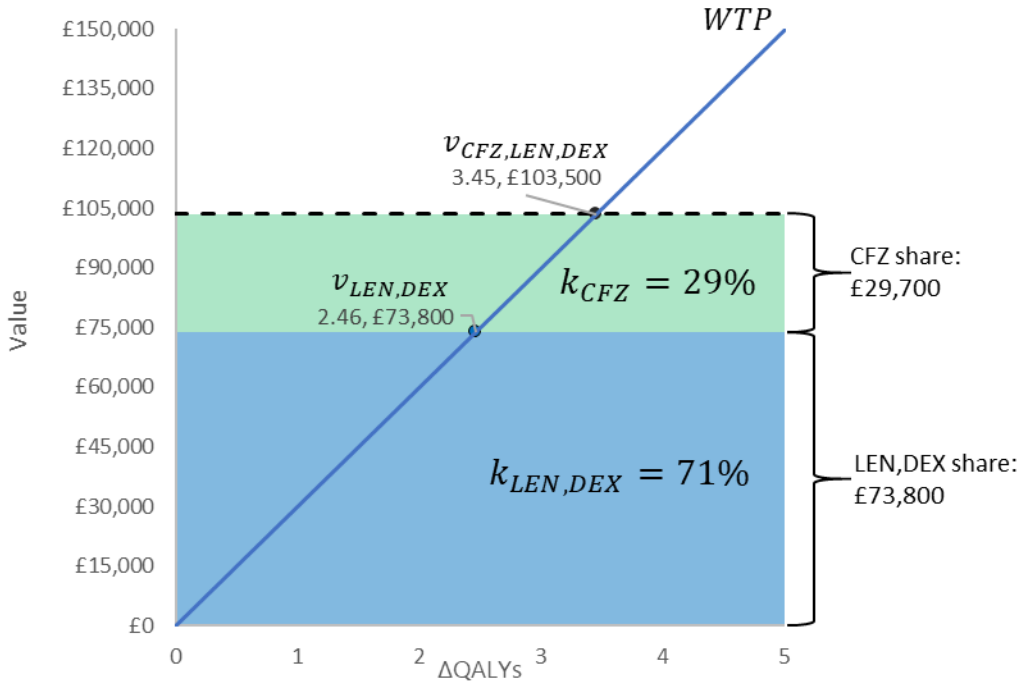
$$k_{LEN,DEX} = \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} = \frac{2.46}{3.45} \approx 71\%$$

$$k_{CFZ} = \frac{Q_{CFZ,LEN,DEX} - Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} = \frac{0.99}{3.45} \approx 29\%$$

This is the same solution that we would obtain if market power were balanced. The resulting values for $k_{LEN,DEX}$ and k_{CFZ} imply that £73,800 of the value of the carfilzomib combination is attributed to lenalidomide plus dexamethasone, and £29,700 is attributed to carfilzomib. This is shown below in Figure 5.10. The value attributed to the backbone therapy, 71%, equals its monotherapy value since we assumed that the combination is additive. The remaining value of the incremental benefit, 29%, attained from treatment with the carfilzomib combination is attributed to carfilzomib.

[22] Note that we set p equal to 0.10 arbitrarily for illustrative purposes only. This implies that the manufacturer of lenalidomide plus dexamethasone may negotiate for an additional $(0.10 \times \frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} \times 100)$ percent of the value of the combination therapy if $\frac{Q_{LEN,DEX}}{Q_{CFZ,LEN,DEX}} < 0.50$.

Figure 5.10. Case Study: Imperfect Information and Balanced Market Power Scenario



Abbreviations: LEN,DEX – lenalidomide and dexamethasone, CFZ,LEN,DEX – combination therapy with carfilzomib plus lenalidomide and dexamethasone, WTP – willingness-to-pay (equals £30,000 per QALY gained).

6. Discussion

This Whitepaper has outlined a potential framework for attributing the value of independent products used in combination. One of the advantages of the framework is that it is independent of price and focuses on the QALY. As is described in section 4.1, it is possible to consider a QALY equivalent of **all** the impacts of a combination product – including any cost-savings. Together, this 'net-QALY' represents the value of a new treatment in health terms and is easily converted to a monetary value by multiplying by the threshold willingness to pay for a QALY. This monetised value of the net-health consequences becomes the maximum (differential) price that the health system should be willing to pay for the combination treatment. Thus, the framework as proposed avoids the complications of judging whether the existing price charged for a product is 'fair' and does not require knowledge of potentially confidential patient access schemes. While users may be unfamiliar with this particular formulation of the cost-effectiveness decision problem, it is a simple rearrangement of the existing decision rules and therefore is entirely consistent with the existing decision-making framework used by HTA bodies such as NICE.

In the case studies presented in section 5, the incremental QALY estimates used are those reported in the corresponding technology appraisal documents without an attempt to include the net-QALY concept identified above. This simplification was judged expedient in the context of this Whitepaper and in light of the fact that the case studies as presented were based only on information publicly available from the technology appraisal documentation. Notwithstanding this simplification in the case studies presented, the generalisability of the framework remains and should not form an impediment to the use of the value attribution formulae as presented. However, further consideration must be given to questions related to the evaluation and selection of clinical evidence such as whether we have 'perfect information' if one of the component therapies has only been studied for a subgroup of the larger population for which the combination therapy is indicated. Treatment patterns and outcomes often vary based on histology and biomarker status, for example, and this introduces additional layers of complexity that we do not consider here.

Overall, the framework requires an accepted health economic model of the combination therapy and its component parts. This modelling exercise will face the usual challenges of evidence synthesis, extrapolation beyond observed data and potentially the use of indirect comparisons. While not to be underestimated, these are the usual tasks required of an economic modelling exercise for a submission to a reimbursement HTA body such as NICE. We have not, therefore, focused on the (considerable) methodological literature describing how these tasks might be conducted. We simply note that the framework presented here does not require any additional modelling beyond that which would be expected for an economic submission.

Although the principles of how to conduct the modelling are standard, a potential practical and legal issue is the need for two independent companies to agree on a core model of the combination product and their respective component therapies that make up the combination. In cases of imperfect information and unbalanced market power, predefining the combination therapy's negotiable share

would be an important but potentially contentious step. The need for agreement is a significant practical hurdle, which is further complicated by existing anti-trust legislation designed to prevent price-collusion that limits the ability of individual companies to collaborate on pricing strategies. This emphasises the importance of the companion 'voluntary arbitration Whitepaper' that provides a road map for negotiations. The framework presented here should be seen as a starting point for those negotiations.

In applying the standard rules of cost-effectiveness analysis, the framework proposed here makes use of the maximum willingness to pay for health gain. The appropriate value of this metric is hotly debated in terms of what is appropriate for a health system to use in guiding its decision making. Is it the (perceived) social value of a QALY? Or is it, as suggested by theory, the value of the marginally displaced intervention in a budget constrained health system? In discussing the framework itself, we conditioned out the value of this threshold. The implicit assumption was that this has already been set by the HTA agency involved; as the case studies presented were based on NICE single technology appraisals, the upper end of NICE's standard WTP threshold of £30,000/QALY were applied. We nevertheless assumed that the price of the two component products would add up to a level that is not supported by the health gains from the combination (at least in the non-synergistic 'sub additive' scenario).

It is worth noting that to implement the framework, cooperation between all parties will be required. It is likely that individual company stakeholders will be asked to accept a price reduction when it comes to the use of their products in combination, at least for many scenarios. We note the additional challenge that arises when one or more component therapies met the criteria to be appraised at a higher WTP threshold, but the combination therapy is appraised at the standard threshold. It is possible that the HTA authority could consider raising the threshold as an inducement for all parties to come to the negotiating table, although discussions emerging from the Bellberry workshop suggest that this approach is unlikely to be implemented in practice [2]. Although the incentive for the backbone manufacturer to participate is vital to the implementation of any solution to the combination medicines issue, and is an important aspect to be discussed as part of the arbitration process, it is beyond the scope of this paper.

Understanding of the issues that make it challenging for combination therapies to demonstrate economic value has deepened considerably since the NICE DSU first showed how clinically effective combination therapies can fail to be cost-effective even if the price of an add-on component equals zero. Many stakeholders have been involved in efforts to identify additional challenges and potential solutions to the problems inherent to valuing and paying for combination therapies. Such stakeholders include the participants at the recent Bellberry workshop, who identified a need for research on methods of value attribution to serve as the basis for pricing negotiations. The Attribution of Value Framework presented in this paper, which has been developed with input from a diverse group of stakeholders, is one such method that we put forth for consideration and discussion.

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