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Methodology

An Attribution of Value Framework for Combination Treatments

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ABSTRACT

Objectives: The use of cost-effectiveness methods to support policy decisions has become well established, but difficulties can arise when evaluating a new treatment that is indicated to be used in combination with an established backbone treatment. If the latter has been priced close to the decision maker's willingness-to-pay threshold, this may mean that there is no headroom for the new treatment to demonstrate value, at any price, even if the combination is clinically effective. Without a mechanism for attributing value to component treatments within a combination therapy, the health system risks generating negative funding decisions for combinations of proven clinical benefit to patients. The aim of this work was to define a value attribution methodology, which could be used to allocate value between the components of any combination treatment.

Methods: The framework is grounded in the standard decision rules of cost-effectiveness analysis and provides solutions according to key features of the problem: perfect/imperfect information about component treatment monotherapy effects and balanced/unbalanced market power between their manufacturers.

Results: The share of incremental value varies depending on whether there is perfect/imperfect information and balance/imbalance of market power, with some scenarios requiring the manufacturers to negotiate a share of the incremental value within a range defined by the framework.

Conclusions: It is possible to define a framework that is independent of price and focuses on benefits expressed as quality-adjusted life-year gains (and/or quality-adjusted life-year equivalents for cost savings), a standard metric used by many health technology assessment agencies to evaluate novel treatments.

Keywords: combination therapies, combination treatments, healthcare, pharmacoeconomics, pricing.

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Highlights

- The challenge of reimbursement and patient access for oncology products used in combination has long been recognized. A paradoxical outcome of this is that add-on therapies to an existing backbone product may not be deemed cost-effective, even if offered at zero cost.
- This article is one of the first contributions to offer a framework for solving the value attribution problem. We acknowledge that the solution offered is not unique, but the framework offers a starting point for negotiations among the manufacturers and payers, which will need to be carefully mediated to avoid compromising the existing competition law.
- The framework allows for value attribution to be based on existing metrics that are used in the reimbursement process but will likely require adjustments to existing prices to meet conventional cost-effectiveness thresholds.

Introduction

The use of combination treatments has been increasing over time with greater scientific understanding of the complex pathophysiology of disease progression. The Association of British Pharmaceutical Industries' members have suggested that as much as half of their oncology medicine pipelines are combination therapies.[1] Because combination treatments can target multiple pathways of a disease simultaneously, they often exhibit greater clinical efficacy than single-agent therapies.[2] This has been evident in the treatment of HIV infection, for example, in which standard use of antiretroviral combination treatments has reduced the rates of disease transmission and increased patient life expectancy.[3,4] Combination treatments have also emerged as mainstay treatments in the field of oncology. A treatment with multiple agents, given simultaneously as a part of a planned course of therapy, often generates a higher therapeutic response and better outcomes for cancer patients.[5] Yet, despite their known clinical benefits, value assessment of novel combination treatments using conventional methods has proved challenging. This can cause combination treatments to receive a not recommended decision and may discourage manufacturers from making health technology assessment (HTA) submissions of combination treatments in which this issue arises. The economic evaluation challenge of combination medicines was discussed in a report by the National Institute of Health and Care Excellence (NICE) Decision Support Unit, which highlighted how combination medicines can fail to be cost-effective even if the novel add-on therapy is provided at zero cost.[6] Therefore, patients in some parts of the world could be unable to access innovative therapies that bring substantial clinical benefits.

Although combination treatments 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 treatments in oncology, a situation which is likely only to get worse given the substantial focus on combination products in the oncology pipeline.[7] Thus, although much of the discussion that follows

will be relevant to combination treatments in many fields, this article focuses on the value assessment of combination treatments in oncology.

A key challenge to value assessment is that combination treatments are commonly approved as a single technology, but their component therapies may be priced independently. The situation is made more difficult when the component therapies are patented and produced by different manufacturers. Manufacturers have control over the price of their own product(s) but not the overall price of the combination if the other combination components are manufactured by a different company. Within the field of oncology, the not cost-effective at zero price scenario discussed in the 2014 NICE Decision Support Unit report often arises in cases which a clinically effective combination treatment is administered until disease progression; therefore, if the use of the combination improves progression-free survival it will lengthen the duration not just of the add-on treatment but also the backbone treatment.[6]

A group of international stakeholders and experts in HTA outlined key challenges and potential solutions to valuing and paying for combination treatments in oncology at an international workshop hosted by Bellberry Ltd in 2019.[8] 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 treatments present to health technology appraisals and for the need to find a solution. Although there was broad support for flexible payment systems and pricing, which were believed to be the most implementable solutions in the near term, there was universal agreement that increasing the willingness-to-pay (WTP) threshold for combinations was not a sustainable solution. The proposed solutions included potential reassessment of the backbone therapy by HTA agencies and payers and revisitation of the prices of component therapies by their respective manufacturers. Participants emphasized 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.

In this article, we propose a value attribution framework for combination treatments. The framework provides a structured method for determining how to attribute the benefit of a combination treatment to each of its components. 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 at various stages from an advisory panel consisting of a broad spectrum of stakeholders, including HTA staff, clinicians, patient experts, 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 article is to facilitate discussion among stakeholders who must work together to ensure that these therapies are available and accessible to the patients who could benefit from their use.

The background to the value attribution problem is presented in more detail in Box 1.[9,10] In the next section, defining characteristics of the problem are given as the potential lack of perfect information and the lack of balance of market power between the backbone and add-on treatments. Against this backdrop, the following section lays out the value attribution framework we propose for the basis of negotiations between stakeholders and a final section offers a discussion of the issues.

Defining Characteristics of the Value Attribution Problem

In the subsections below, we discuss 2 defining features of the value attribution problem: (1) imperfect information and (2) imbalance of market power.

Imperfect Information

The health outcome generated by a combination treatment 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 arguably unknown. In some cases, component therapies will have been studied independently in phase III clinical trials for the indication in question. In these cases, we can use what we know about the health benefits generated by each therapy independently to apportion the value derived from the combination treatment. In many cases, however, the independent value of component treatment will not be known. Many treatments are developed specifically to work in tandem with another and as such may be authorized for use only within the combination. With the possible exception of early-stage clinical studies to establish the pharmacodynamic properties of the treatment 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 in which the independent benefit of 1 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 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 treatment is being assessed. It is more difficult to solve the value attribution problem in scenarios where there is imperfect information.

Imbalance of Market Power

When all the component treatments are produced by a single manufacturer, the manufacturer has full control over pricing decisions. However, when component treatments are produced by different manufacturers, price coordination is forbidden through strict anticompetition laws. Antitrust regulation prohibits different manufacturers from working together explicitly to make pricing decisions. 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.[5] Flexibility in the pricing of the backbone therapy may depend on its current stage in the product life cycle, if it is approved for multiple indications and whether it remains under patent and for how long. If a backbone therapy has many years left under patent or is used in multiple indications, 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 variation of prices across indications. If a backbone therapy is approved for multiple indications and the market does not allow price or discount variation by indication or nonuniform pricing, its manufacturer may have little incentive to reduce its price. Here, any reduction in price will reduce revenue across all indications. The manufacturer of the add-on therapy may be forced into setting a lower price so that the combination treatment will be cost-effective or need to completely withdraw the combination

BOX 1. Background to combination therapies and the value attribution problem.

A combination treatment combines 2 or more individual component treatments to treat a single disease. Many combination treatments comprise a backbone treatment and 1 or more add-on treatments. A backbone treatment is a drug or drug combination that is already approved for use and is well established before being used in combination with another treatment. Backbone treatments often become standard of care for a given disease. An add-on treatment is a drug or set of drugs that is added to an existing backbone treatment: it may have been developed and introduced into the market as an independent treatment, or it may have been developed specifically to work in combination with the backbone treatment. 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 treatment that includes an add-on treatment can become a backbone therapy as the standard of care changes over time and that combination products may include triplet and even quadruplet treatments. Nevertheless, the passage of time will likely mean that some components of combination treatment will be out of the exclusivity period that is granted to new treatments. Hence the focus in this manuscript is on the use of 2 patented products in combination in which the main issue of pricing component treatments lies.

Component treatments 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 epitopes. Their combined use thus provides dual blockade of human epidermal growth factor receptor 2 signaling pathways, which translates into improved survival for patient.[9] Similarly, combination treatments may generate better health outcomes because the activity of one component treatment 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 antitumor activity when they are used in combination to treat programmed death-ligand 1 positive advanced or metastatic nonsmall cell lung cancer without epidermal growth factor receptor or anaplastic lymphoma kinase tumor mutation.[10]

Novel therapies and technologies are subject to rigorous economic assessment to optimize the allocation of finite healthcare budgets. One method that is commonly used to assess the economic value of new interventions is CEA. This approach assesses value based on how changes in healthcare costs correlate to changes in health outcomes. The 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 and CEA using the QALY (often termed as CUA) is a framework that has been adopted by many health technology assessment authorities across the world (for example, Australia, Canada, Denmark, Sweden, The Netherlands, and the United Kingdom) and typified by the NICE in the United Kingdom.

Combination treatments are clinically important for the treatment of diseases with complex pathophysiological processes such as cancer. For patients to have access to these potentially beneficial treatments, combination treatments must be priced commensurately with their value as measured by accepted WTP thresholds for a QALY. Yet, when combination treatments are composed of individual drugs that are priced independently, the cost of the combination may lead to a cost-effectiveness ratio that exceeds the WTP threshold. This occurs because (1) the prices of component therapies that have been approved previously 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 because of the longer duration of treatment.

For NICE in the United Kingdom, the not cost-effective at 0 price paradox is exacerbated when the backbone therapy meets end-of-life/severity criterion at the time of its appraisal, qualifying the backbone for a modifier to the usual cost-per-QALY decision rule, but the combination treatment fails to qualify. This scenario may arise because life expectancy before the introduction of the backbone therapy was shorter, 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/severity criterion. In these cases, it is especially challenging for a combination treatment to be considered cost-effective at the standard WTP threshold because there is even less room for the additional cost of the add-on therapy. For combination treatments to meet an existing WTP threshold for cost-effectiveness, it is likely that the prices of component treatments will need to be reduced. To address the question of how this cost reduction should be shared, we must determine how much of the value of the combination treatment should be attributed to each of its component treatments.

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 difficult to quantify. Practical implementation is further hampered because even the independent clinical benefits of component therapies are often unknown. When component therapies are produced by different manufacturers, any imbalance in market power creates potential winners and losers (either compared with the status quo or, indeed, to a perception of what could be achieved) adding yet further complexity. In the case of a combination treatment that is formed by combining an existing backbone therapy with a novel add-on, the balance of power will often be tilted toward the manufacturer of the backbone therapy. This occurs in part because the combination treatment and its backbone therapy are appraised independently. Once a backbone therapy has been appraised and approved by a health technology assessment, it is not automatically involved in the appraisal of the combination treatment, which will be fully sponsored by the manufacturer of the add-on therapy. Therefore, the manufacturer of the existing therapy may not have an incentive to revisit the price of its own product and participate in negotiations related to value attribution. The common scenario of different manufacturers also presents competition problems because many are competitors in the same therapeutic area, meaning that pricing and dialog between manufacturers is subject to competition law.

CEA indicates cost-effectiveness analysis; CUA, cost-utility analysis; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; WTP, willingnesss-to-pay.

should the cost-effective price not be commercially viable as a result. In this scenario, the manufacturer of the add-on therapy bears the full cost of developing the combination treatment but captures limited value.[2,11] In contrast, the manufacturer of the backbone therapy captures additional value from the combination treatment without bearing new costs.

Value Attribution Framework

In laying out our proposed solution to the problem of value attribution we consider the 4 scenarios that are characterized by the existence of full information or incomplete information on the monotherapy value of the component treatments and by the presence or absence of power imbalance between the component manufacturers.

We adopt a definition of value that is based on the net-equivalent quality-adjusted life year (QALY), which is a simple rearrangement of the standard cost-effectiveness/net-benefit expressions that excludes the cost of the pharmaceutical products. This is laid out in Box 2.[12-14] In Box 3 we build on this to introduce the notation for the proposed solutions.

Consider the combination treatment with component treatments B and A. (We present the framework using the simple case of a combination treatment consisting of 2 components. However, the framework can also be applied to combination treatments with more than 2 components. In the latter case, one or both of therapies B and A will be combination treatments consisting of more than 1 component.) Let k_B be the proportion of the value of the combination treatment that is attributed to backbone treatment B and let k_A be the proportion of the value that is attributed to add-on treatment A. Here, we present a framework for selecting values for k_B and k_A that accounts for differences in the clinical effectiveness of treatments B and A (measured in terms of incremental QALYs compared to standard of care), as well as the balance of market power and satisfies the following basic requirements for a satisfactory value attribution rule: (1) each component should receive a positive share of value; (2) shares of value should sum to unity; (3) that greater market power should lead to retaining a greater share of value; (4) has consistency with the standard rules of cost-effectiveness analysis, and; (5) can be estimated with existing information that would be included in a typical reimbursement dossier. Note that the explicit WTP threshold for the value of a QALY is required to operationalize the framework, but the valuation of the combination using whatever WTP threshold is appropriate is a necessary first step but is separable from the second step of attributing that value to the component treatments.

Perfect Information and Balance of Market Power

The simplest scenario is one in which there is perfect information and balanced market power. In this scenario, we use what we know about the incremental benefits attained from

BOX 2. The net-equivalent quality-adjusted life-year (QALY) value based on standard cost-effectiveness concepts.

Standard health economic decision rules dictate that an intervention should be implemented over a comparator if its incremental health benefits justify its incremental cost.[12] The ICER is the statistic that is used to summarize this value and is defined as the incremental costs (ΔC) divided by incremental benefits (ΔE). When QALYs are used 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 with a maximum willingness to pay 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 (ΔNHB) whereby the new technology is adopted if its ΔNHB is greater than 0[13]:

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

Weinstein and Stason describe how the incremental costs and effects attributable to implementing a healthcare intervention compared with a relevant comparator can be disaggregated into constituent parts[14]:

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

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):

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

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 ΔQ), 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 because the value on the left-hand side of the equation is a QALY equivalent, the framework can be used using only the differences in the QALY measure alone or using the net-equivalent QALYs, which include cost-differences transformed to the QALY scale. This is important because it allows the framework to be applied without reference to the price of component products.

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

BOX 3. Notation for the value attribution solution and subadditive versus synergistic benefits.

Let Q_B and Q_A be the net-equivalent QALYs attained from monotherapy with a backbone treatment B and an add-on treatment A, respectively, and Q_{AB} be the net-equivalent QALYs attained from both treatments used in combination. These health outcomes reflect the additional QALYs gained relative to a common standard of care comparator.
The monetary value of treatments B and A used as monotherapy and in combination treatment are obtained by multiplying the respective net-equivalent QALYs by the WTP threshold:
$v_A = \lambda \cdot Q_A$
$v_B = \lambda \cdot Q_B$
$v_{AB} = \lambda \cdot Q_{AB}$.
We say that a combination treatment is additive when the incremental benefit it generates equals the sum of the incremental benefits that each of its component treatments generate when used independently in the same indication, against the same comparator. That is, a combination treatment consisting of A and B is additive when the following relation holds:
$Q_{AB} = Q_A + Q_B$.
A feature of combination treatments that makes value attribution challenging is that their efficacy is often less than additive in practice. In cases which the monotherapy effect of each component treatment is known, we often observe that their use in combination is strictly subadditive in that the incremental benefit generated by the combination is less than the sum of the incremental benefits of each component treatment when used alone. The following relation holds for strictly subadditive combination treatments:
$\max(Q_A, Q_B) < Q_{AB} < Q_A + Q_B$.
Combination treatments may also be synergistic, as described in section 2.1. 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 because in this case $v_{AB} > v_A + v_B$. In this scenario, there is potential for more than one winner and no losers. We note that in cases which we have imperfect information about the independent benefits of component therapies, we cannot say with certainty whether a combination treatment is additive, strictly subadditive, or synergistic.

QALY indicates quality-adjusted life year; WTP, willingness to pay.

monotherapy treatment with each of the components to select k_B and k_A. 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:

$$k_B = \frac{Q_B}{Q_A + Q_B} \text{ and } k_A = \frac{Q_A}{Q_A + Q_B} \quad (1)$$

Figure 1A illustrates the strictly subadditive case. Because $Q_{AB} < Q_A + Q_B$, it follows that $v_{AB} < v_A + v_B$. The height of the region shaded in blue represents the monotherapy value of the backbone and the region shaded in green represents the monotherapy value of the add-on. 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 treatment is given by the dashed line in Figure 1A. The left panel of Figure 1A shows that the sum of the monotherapy values of the component drugs exceeds the WTP for the incremental benefit generated by the combination treatment.

The right panel of Figure 1A also shows that, in this case, the solution can also be interpreted as multiplying each independent value by a common factor defined as

$$s = \frac{Q_{AB}}{Q_A + Q_B}.$$

The solution for a scenario in which there is perfect information, and no imbalance of market power thus can be considered either as attributing the value of the combination in proportion to the known monotherapy benefits or as applying a common factor to the independent treatment values. This is shown in the right panel of Figure 1A above as a shrinkage factor due to the subadditive nature of the combination benefit illustrated, although the solution works for any level of additivity.

Perfect Information and Imbalance of Market Power

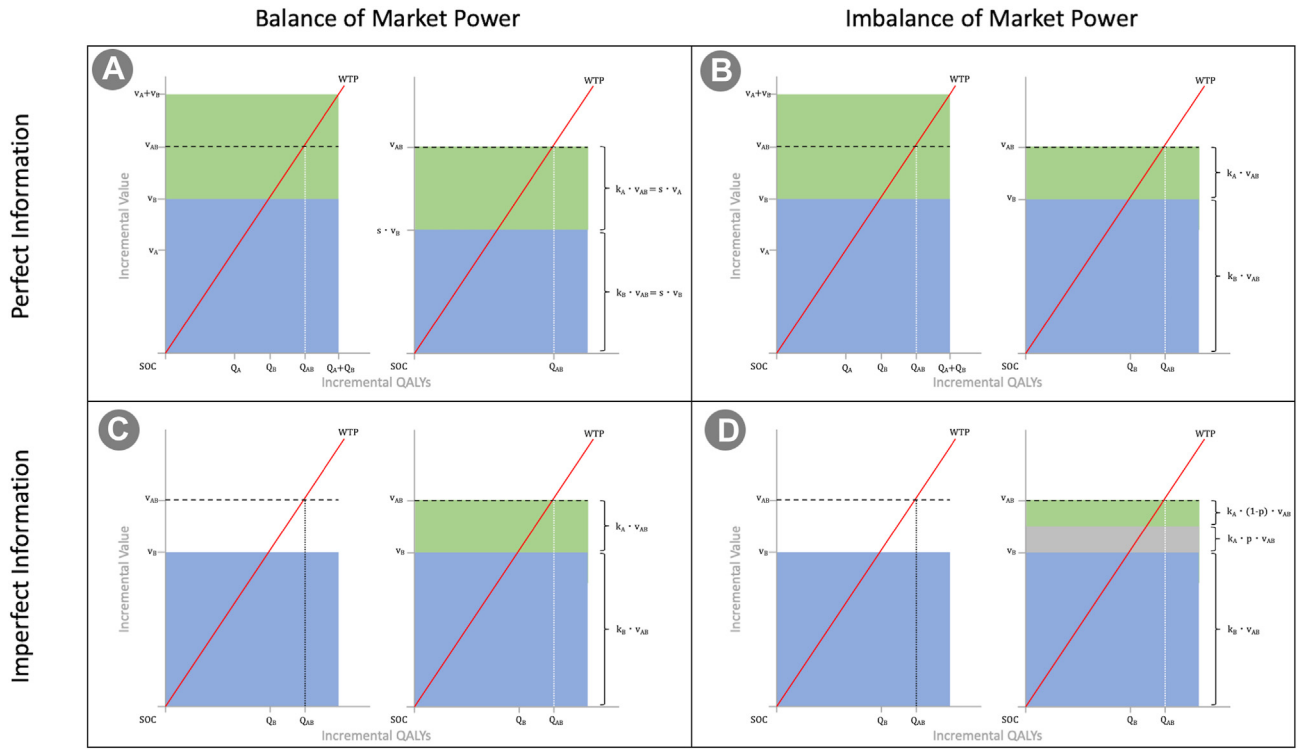
Suppose that treatment B, the backbone therapy in the combination, was licensed and reimbursed on the market before the introduction of an add-on treatment A. Because the manufacturer of B has the "first-mover advantage" and no legal obligation to drop/renegotiate their price, it has less incentive to accept a share of the value of the combination that is less than the monotherapy value of treatment B. The value attributed to the backbone treatment will equal its monotherapy value (recall that the value attribution framework proposed does not reference existing prices. Equating the value of treatment B in combination to its monotherapy value could imply a price reduction if the combination product leads to an increase in the quantity of treatment B that is utilized.) if k_B and k_A are chosen as follows:

$$k_B = \frac{Q_B}{Q_{AB}} \text{ and } k_A = \frac{Q_{AB} - Q_B}{Q_{AB}}.$$

This is true because $\frac{Q_B}{Q_{AB}} \cdot v_{AB} = v_B$. When the combination treatment is strictly subadditive, the value attributed to the backbone treatment B will be greater under this solution compared with the solution for the perfect information scenario in which there is no imbalance of market power.

However, if the combination treatment is synergistic, then the value attributed to treatment B when $k_B = \frac{Q_B}{Q_{AB}}$ would be less than the value it would be attributed if $k_B = \frac{Q_B}{Q_A + Q_B}$. Recall that the overall QALY gain is larger for synergistic combinations, because $Q_{AB} > Q_A + Q_B$. This, in turn, implies that $v_{AB} > v_A + v_B$ such that the value attributed to each component therapy could exceed its respective monotherapy value. Thus, attributing to treatment B its monotherapy value in the case of synergistic benefits of combination means that the add-on treatment A receives all of the value in excess of $v_A + v_B$. We therefore assume that when there is an

Figure 1. Value attribution solution for scenarios of (A) perfect information and balanced market power; (B) perfect information and imbalanced market power; (C) imperfect information and balanced market power; and (D) imperfect information and imbalanced market power.



Panels (A) and (B) show the strictly subadditive case. On the left side of each panel, the height of the regions shaded in blue represents the monotherapy value of the backbone and the region shaded in green represents the monotherapy value of the add-on. For panels (C) and (D), the value of the add-on therapy is unknown. The right side of each panel shows the value attributed to each of the backbone and add-on treatments under our proposed solutions. The gray rectangle in panel (D) represents the negotiable share of the value of the combination treatment. In this example, the size of the negotiable share, p, is set to 50% of the share that would be attributed to the add-on treatment if market power were balanced. The maximum WTP for the incremental benefit generated by the combination treatment is given by the dashed line.

imbalance of market power, the manufacturer of the backbone therapy will leverage that power to select the solution that maximizes its share of the value. The solution in this scenario is thus the following:

$$k_B = \max\left(\frac{Q_B}{Q_{AB}}, \frac{Q_B}{Q_A+Q_B}\right) \text{ and } k_A = \min\left(\frac{Q_{AB}-Q_B}{Q_{AB}}, \frac{Q_A}{Q_A+Q_B}\right), \quad (2)$$

where *max* and *min* are functions that return the maximum and minimum values, respectively, of the parameters contained within the parentheses. A greater share of the value of the combination is attributed to the backbone drug, treatment B, when market power is imbalanced than when there is no imbalance of market power. Consequently, a lower share of the value of the combination is attributed to the add-on drug, treatment A, when market power is imbalanced compared with when it is balanced. This is shown below in the right panel of Figure 1B for the subadditive case (c.f. Fig. 1A). Note that the height of the blue rectangles shown in the left and right panels of Figure 1B are equal. This illustrates that the share of the value of the combination treatment that is attributed to backbone treatment B is equal to its value as a monotherapy and consequently the add-on treatment A receives value corresponding only to the incremental benefit of the combination treatment.

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. As a consequence, we cannot know whether the combination is strictly subadditive or synergistic because we do not know the independent benefit of the new add-on drug. Our proposed solution attributes the incremental value of the combination treatment to A, such that:

$$k_B = \frac{Q_B}{Q_{AB}} \text{ and } k_A = \frac{Q_{AB}-Q_B}{Q_{AB}}. \quad (3)$$

Figure 1C illustrates the case of a combination treatment in which the available information is imperfect, but market power is balanced. The independent value of the backbone drug, treatment B, 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 treatment is given by the dashed line in the figure. Because information is imperfect, we do not know the value of treatment 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 $Q_A = Q_{AB} - Q_B$ 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 1C. The value attributed to the backbone therapy then equals its monotherapy value as it did in the previous example. Note that this solution does not require an assumption of additivity but is consistent with Eq. (1) if the additivity assumption holds.

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. This is the most encountered scenario in a real-world setting. As shown above, the value attributed to the backbone therapy will be greater when there is an imbalance of market power compared with when there is no imbalance of market power, all else equal. We would expect the same logic to hold in the present scenario, in which there is imperfect information and an imbalance of market power. The manufacturer of the backbone therapy would favor a solution where $k_B > \frac{Q_B}{Q_{AB}}$. The solution to the scenario in which 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_B and k_A will fall within the following ranges: $\frac{Q_B}{Q_{AB}} \leq k_B < 1$ and $0 < k_A \leq \frac{Q_{AB}-Q_B}{Q_{AB}}$, with $k_A + k_B = 1$. This is equivalent to saying that the imbalance of market power would encourage the backbone treatment manufacturer to negotiate a share of the add-on treatments incremental value.

This negotiable share of the incremental value offered by the combination treatment can be defined as a proportion p such that if $p = 0$ then $k_B = \frac{Q_B}{Q_{AB}}$ and $k_A = \frac{Q_{AB}-Q_B}{Q_{AB}}$ (Soln. 3), but if $p = 1$ then the entire value of the combination is attributed to the backbone treatment B and the add-on treatment A receives 0 value. A more general solution for the imperfect information scenario is thus given below, with $p \neq 0$ when there is an imbalance of market power.

$$k_B = \frac{Q_B}{Q_{AB}} + p \cdot \frac{Q_{AB}-Q_B}{Q_{AB}} \text{ and } k_A = (1-p) \cdot \frac{Q_{AB}-Q_B}{Q_{AB}} \quad (4)$$

Despite the logical constraints offered by $0 \leq p \leq 1$, there is a danger that such a wide range of values is unhelpful as a solution to the value attribution problem. We therefore propose that p might be predefined, and for the purposes of illustration here, we take the midpoint of 50% as the preferred value of p in the solution above.

Figure 1D illustrates how the solution for a scenario in which there is imperfect information and an imbalance of market power differs from that for the scenario in which there is imperfect information, but market power is balanced. In the figure, k'_A and k'_B represent the solution to the balanced market power scenario (Eq. [3]). (We can thus rewrite (Eq. [4]) as $k_B = k'_B + p \cdot k'_A$ and $k_A = (1 - p) \cdot k'_A$.) The gray rectangle in Figure 1D represents the negotiable share of the value of the combination treatment. In this example, the size of the negotiable share, p, is set to 50% of the share that would be attributed to the add-on treatment if market power were balanced.

Summary of the Four Solutions

The 4 solutions identified in the article are summarized in Table 1 together with a brief textual description of the solution.

In the White Paper that was published for consultation and which provides a more detailed description of the solutions described here, we include a case study for each of the solutions.[15] Because these case studies are based on published data that did not include detailed information allowing calculation of net-equivalent QALYs as described in section 3.1 above, the case studies presented are based on QALY outcomes only.

Discussion

This article 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 3.1, 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 WTP for a QALY. This monetized 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. Although 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

Table 1. Summary of the value attribution solutions by information/market power scenarios.

Scenario	Backbone share: k_B	Add-on share: k_A	Description
Perfect information and balanced market power			
	$\frac{Q_B}{Q_A+Q_B}$	$\frac{Q_A}{Q_A+Q_B}$	In proportion to monotherapy outcomes
Perfect information and imbalanced market power			
	$\max\left(\frac{Q_B}{Q_{AB}}, \frac{Q_B}{Q_A+Q_B}\right)$	$\min\left(\frac{Q_{AB}-Q_B}{Q_{AB}}, \frac{Q_A}{Q_A+Q_B}\right)$	Add-on gets the incremental value if subadditive; in proportion to monotherapy outcomes if synergistic
Imperfect information and balanced market power			
	$\frac{Q_B}{Q_{AB}}$	$\frac{Q_{AB}-Q_B}{Q_{AB}}$	Add-on gets the incremental value
Imperfect information and imbalanced market power			
	$\frac{Q_B}{Q_{AB}} + p \cdot \frac{Q_{AB}-Q_B}{Q_{AB}}$	$(1 - p) \cdot \frac{Q_{AB}-Q_B}{Q_{AB}}$	Add-on and backbone negotiate a share of the incremental value

decision-making framework used by HTA bodies such as the NICE in the UK.

Overall, the framework requires an accepted health economic model of the combination treatment and its component parts. The ideal evidence to support such a model and the value attribution approach proposed here would be a randomized controlled trial with 3 arms in which each component treatment is used as monotherapy and tested against the combination. This modeling exercise will face the usual challenges of evidence synthesis, extrapolation beyond observed data, and likely the use of indirect comparisons to compare any monotherapy evidence with the combination evidence. Although not to be underestimated, these are the usual tasks required of an economic modeling 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 (such as the comparability of the evidence in any indirect treatment comparisons, for example). We simply note that the framework presented here does not require any additional modeling beyond that which would be expected for an economic submission for reimbursement.

Although the principles of how to conduct such modeling are standard, a potential practical and legal issue is the need for 2 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 treatment'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 antitrust legislation designed to prevent price collusion that limits the ability of individual companies to collaborate on pricing strategies. The framework presented here should be seen as a starting point for negotiations that are arbitrated in such a way as to comply with antitrust laws.

In applying the standard rules of cost-effectiveness analysis, the framework proposed here makes use of the maximum WTP 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. In practice, although many countries make use of the QALY and cost-utility analysis to inform reimbursement decisions the existence of a clearly defined cost-per-QALY ratio for decision making is less frequent. We nevertheless assumed that the price of the 2 component products would add up to a level that is not supported by the health gains from the combination (at least in the nonsynergistic subadditive scenario).

It is worth noting that to implement the framework, cooperation between all parties will be required. It is likely that individual company stakeholders may 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 1 or more component therapies met the criteria to be appraised at a higher WTP threshold, but the combination treatment is appraised at the standard threshold. This could arise, for example, if the original therapy previously met the end-of-life criteria or subsequently meets the new severity criteria that have been used by NICE, but the combination treatment does not (perhaps because of the availability of the backbone treatment). It is possible that the HTA authority could consider raising the threshold as an inducement for all parties to come to the negotiating table. The willingness of the backbone manufacturer to accept a negotiated value attribution price reduction may depend on the context. As highlighted in section 2.3.2, in which a jurisdiction does not allow for indication-specific pricing, and the backbone treatment is used across more indications than the specific indication of the combination therapy, they are less likely to accept a price reduction. 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 article.

The proposed framework outlined in this article does not offer a unique solution to the value attribution problem and does not make any claims concerning optimality. Other assumptions, particularly concerning the balance of power and information between the actors, including not only the manufacturers but also the reimbursement authorities, could lead to different solutions.

This article is based on a White Paper that was published for public consultation in 2021.[15] At the time of publication, the value attribution framework proposed here was the first value attribution method proposed to solve the not cost-effective at 0 price paradox. We are aware of other solutions to the value attribution problem, in particular, a working article by the UK Office of Health Economics has recently been published with an alternative approach to value attribution.[16] Our view is that there is no single solution to the value attribution problem; therefore, we welcome new approaches or further refinement of the framework we present here.

Conclusion

Our belief is that, in the absence of a single agreed approach to the value attribution problem, alternative solutions can reinforce one another to show the likely set of solutions that can pave the way for a negotiated solution. Such a solution is urgently required, and it is incumbent upon all stakeholders to come together to enact that solution so that patients gain access to the most effective treatments available at a price that is fair and sustainable.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

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