Voluntary Arbitration Framework for Combination Therapies

A proposed process by the Voluntary Arbitration Working Group

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Contents

Executive Summary

The use of combination treatments has been increasing over time with greater scientific understanding of the complex pathophysiology of disease. As combination treatments target multiple pathways and levels of a disease simultaneously, they exhibit greater clinical efficacy than single-agent treatments [1]. This has been evident in the treatment of HIV infection, for example, where standard use of antiretroviral combination treatments has reduced rates of disease transmission and increased patient life expectancy [2]. Combination treatments have also emerged as a mainstay in the field of oncology. Treatment with multiple agents using a different mechanism of action often generates a higher therapeutic response and better outcomes for patients [3]. Yet despite their known clinical benefits, value assessment of novel combination treatments can often be challenging. This can cause negative funding decisions for combination treatments or may discourage manufacturers from making Health Technology Assessment (HTA) submissions of combination therapies. As a result, patients could be unable to access safe and effective therapies which could bring substantial clinical benefits.

A key challenge to value assessment is that a treatment combination is evaluated as a single technology, but the component treatments are priced independently. The situation is made more difficult when the component treatments that form a combination are patented and produced by different manufacturers. Manufacturers only have control over the price of their own treatments and not over the overall price of the combination.

Different stakeholders have published on the issue of combination treatments in recent years, especially regarding the challenges around methods to attribute value to the component parts of the combination. However, a distinct but vital issue in addition to value attribution, is how manufacturers, who may be competitors in other indications, can discuss and share information from the attribution in a compliant manner, without breaching competition law.

Current literature shows that all stakeholders: government, HTA bodies, payers, clinicians, and manufacturers, agree that a fair, implementable and transactable solution needs to be found [4-6]. Takeda UK Limited 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 it raised. In 2019, Takeda established an Advisory Group that was tasked with designing transactable and implementable solutions to the problem of appraising combination treatments. The group was made up of experts from economic, clinical, patient advocacy, academic and legal communities. In addition, input on the requirements and parameters of a transactable solution were received from NHS England and NICE. Based on this feedback and expertise within the Advisory Group, two distinct but interlinking frameworks were developed outlining a comprehensive proposed solution to combination treatments:

1. An Attribution of Value Framework to allocate value to each component of the combination
2. A Conceptual Framework and Standard Operating Procedure (SOP) for an arbitration process which considers competition law

In this Whitepaper, the results of the second workstream proposing a Framework and procedure for the arbitration process considering competition law are presented. An accompanying Whitepaper outlining a proposed economic value attribution methodology, named *An Attribution of Value Framework for Combination Therapies,* was published in January 2021 [7].

The proposed Voluntary Arbitration Framework and SOP presented in this Whitepaper initially explores the background to the challenge of combination treatments, the current consequences due to the challenge and the need for a transactable solution to be developed. The Whitepaper then defines the fundamental requirements of any solution based on multi-stakeholder expert input. The requirements are: (i) must deliver improved patient access to combination treatment, (ii) must be compatible with

existing HTA methods and processes, (iii) must address competition issues and (iv) must encourage manufacturers to work together. For the purposes of this Whitepaper, England is used as the reference country therefore NICE methods and process form the basis for the Framework and SOP; the proposed solution therefore adheres to existing cost-effectiveness thresholds.

The Whitepaper proposes the concept frequently used in mergers and acquisition, *clean teams*, as a way to address the competition law issues with intercompany dialogue. The Authors propose the use of external *clean teams* to discuss and agree on the value attributed to each component treatment as a mechanism of decreasing the risk of a competition law breach by separating the information shared during the Arbitration from the rest of either manufacturer's wider business.

In addition to the use of *clean teams*, the appointment of an independent arbitrator is proposed. The arbitrator would be responsible for facilitating the Voluntary Arbitration process, using their expertise to ensure it is used appropriately and in a timely manner aiming to minimise any delays to the parallel NICE Single Technology Appraisal (STA) of the combination. The Arbitrator would increase transparency of the process, provide additional de-risking of potential competition breaches, and may act to issue a recommended outcome in the event of an impasse.

Due to requirements of competition law and manufacturer participation, the Authors argue that non-uniform pricing is required in the exceptional and unique challenge posed by combination treatments. The Authors do however stress that this flexibility should be ring-fenced to combinations undergoing the Voluntary Arbitration, and the final mechanism be simple and transactable. Additionally, while we consider participating in the process should be mandatory, the outcome should be non-binding and either party would retain the right to walk away from the process. This would be important to encourage companies to be willing to support the solution however, in the spirit of transparency, the Authors also support public disclosure of the progress of discussions, including should the manufacturers decide to withdraw. Another important principle is that the solution and participating companies take a long-term view meaning that over time companies may experience being both the 'driver' and 'passenger' in the process.

Whilst the above are specific details of the proposed solution they all sit under a detailed SOP, describing how each of these elements align with the existing NICE STA process and timeline.

The proposed solution, described over the two Whitepapers, is thought to be the first comprehensive solution covering both the economic value attribution and a practical implementation framework for outlining how inter-company discussions could be conducted in a compliant manner. By taking the approach to develop a solution from the ground up, starting with a thorough examination of the issue and restrictions faced by each party affected. The Framework was developed with the aim of mitigating these issues; each proposed element of the Voluntary Arbitration Framework works to address an identified issue in a complementary manner. A key strength of the proposed solution is that it was co-created by multiple stakeholders, all of whom have different needs and perspectives, so that the proposed framework is acceptable by the key parties. By taking this bottom-up and co-creation approach as well as by seeking input from key external stakeholders, the Authors hope to have a proposal which is implementable and transactable.

Despite efforts to create a solution which addresses the many issues of combination treatments, and at the same time aligning to current NICE and NHSE methods and processes, there are outstanding challenges and limitations. As such a discussion section has been included where key questions are posed to readers for further consideration. Additionally, feedback and debate regarding outstanding challenges and limitations is welcomed and indeed encouraged. Please send any questions and comments to combinationmedicinesUK@takeda.com.

1. Background

In 2014, the Decision Support Unit (DSU) for the National Institute of Health and Care Excellence (NICE) – the National Health Technology Assessment (HTA) organisation for England and Wales – published a paper that outlined the circumstances in which health technologies that are demonstrated to be clinically effective, but which struggle to demonstrate cost-effectiveness [5]. 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 treatment to fail to be cost-effective even if the price of the add-on treatment equals zero.

In 2017, Takeda UK held a roundtable meeting with representatives from NICE, National Health Service England (NHSE), the Association of British Pharmaceutical Industry (ABPI), economists, members of parliament and patient and clinical communities. The aim of this meeting was to gain an understanding of the cost-effectiveness of combination treatments, as well as the challenges of access to them from multiple different perspectives. During this roundtable it was noted that increasingly complex combination treatments are being developed across various diseases, including cancer, and that combination treatments make up a significant proportion of treatments in the pipeline. It was also noted that combinations often struggle to get reimbursement approval. The introduction of combination treatments into the treatment pathway is therefore either delayed, restricted or does not happen at all. In certain circumstances, this issue has led to manufacturers opting not to enter into the appraisal process of a combination treatment. There was a strong consensus among all participants that the issue of demonstrating cost-effectiveness with combination treatments is important and expected to increase. Participants also concluded that there is a pressing need for a solution.

In July 2018, the Amyloidosis Research Consortium UK (ARC UK) also organised a meeting to address the issue of demonstrating cost-effectiveness with combination treatments [8]. A round table meeting was convened to bring stakeholders together to present, discuss and debate potential solutions. It was recognised that some of the problems could be mitigated by better, and more strategic, value creation upstream of the assessment process. However, the existing problem for combination treatments which were near to HTA appraisal would require a bespoke solution. Various solutions were presented and discussed.

From these discussions, the concept of voluntary arbitration between the manufacturers of the combination components emerged as preferred potential solution. Voluntary arbitration would allow/assist manufacturers to come to a mutually accepted allocation of the current willingness-to-pay (WTP) thresholds based on an economic value attribution. The stakeholders further noted that any solution would need to be compatible with existing appraisal, pricing and reimbursement methods, processes and policies, as well as existing competition laws around inter-company dialogue, particularly as it pertains to pricing. It was also agreed that all implicated stakeholders should be involved in co-creating these potential solutions to increase the likelihood of their acceptance and use.

In 2019 the Voluntary Scheme for Pricing and Access (VPAS) made reference to and acknowledged the challenges in assessing combination treatments. In doing so, the Department of Health and Social Care (DHSC) said it would welcome solutions. The VPAS suggests that industry take the lead role in the development of any potential solution [9].

The problem of demonstrating cost-effectiveness with combination treatments and the urgency to find a solution is not limited to the UK, as was highlighted by the Bellberry Group, who brought

international experts in health technology assessment (HTA) together in late 2019 to outline the challenges and potential solutions to valuing and paying for combination treatments in oncology [4]. The stakeholders represented a diverse set of perspectives from across the world from HTA agencies, the clinical community, academia, patients, and the pharmaceutical industry.

The proposed solutions from the Bellberry Group meeting included potential re-assessment of the backbone treatment by payers and re-visitation of the prices of component treatments by their respective manufacturers. There was broad support for flexible payment systems and pricing, which were believed to be the most implementable solutions in the short-term [4].

Participants emphasised that implementation of any solution would require an accepted method for attributing the value of a combination to its component treatments. 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. However, there was no discussion or consideration given to the process (and the subsequent framework) that would be needed for industry to discuss and implement the attribution of value and its implication on pricing in an appropriate and legally compliant way.

Following the 2018 ARC UK roundtable meeting, Takeda UK initiated a project to develop proposed solutions, with the involvement of a multi-disciplinary Advisory Group consisting of a broad-spectrum of stakeholders, including clinicians, academics, policy & competition experts and patient advocacy. In addition, input on the requirements for a transactable solution was sought from NHS England and NICE. Based on this feedback and the expertise within the Advisory Group a proposed solution was developed consisting of two complementary components; i) an economic value attribution of component treatments and ii) a framework which would allow for voluntary arbitration between manufacturers.

This Whitepaper focuses on the latter; how a voluntary arbitration process could be put into practice under a structured framework and standard operating procedure (SOP), which would enable intercompany dialogue between manufacturers of the combination treatment components, alongside existing HTA and commissioning processes. It is designed to sit alongside its sister Whitepaper, *A Value Attribution Framework for Combination Therapies* [7], which provides an economic methodology for attributing the benefit of a combination treatment across each of its component parts.

Although this Whitepaper is focused on the UK, specifically England, and represents the HTA processes and legal frameworks of this jurisdiction, the authors believe the core components of the proposed framework could be replicated and adapted to any cost-effectiveness market and disease area.

In this Whitepaper the authors present the challenge posed by combination treatments, explore the issues in the context of the criteria that need to be considered, and finally go on to outline the proposed Voluntary Arbitration Framework.

This is followed by a discussion which outlines some of the challenges with the proposed framework and discusses potential ways of overcoming these. The Whitepaper concludes by seeking feedback from all stakeholders impacted by the HTA of combination treatments.

2. The issue

2.1 Definition of combination treatments

A combination treatment combines two or more individual component treatments into a single treatment regimen used to treat a disease. Many combination treatments are comprised of a "backbone" treatment and one or more "add-on" treatments. A backbone treatment is a single treatment or treatment combination that is already approved for use and whose market share and use in clinical practice is usually already well-established. These backbone treatments are often the existing standard of care for a given disease.

An add-on treatment is a single treatment or treatment combination that is added to an existing backbone treatment. It may have been developed and introduced onto 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 programme and registrational trials would likely have been conducted with the combination treatment only. We note that what is an add-on treatment today, can become a backbone treatment as the standard of care changes over time. An add-on treatment may be developed by the same manufacturer as the backbone treatment, or more commonly, by a different manufacturer.

A combination treatment may exhibit greater clinical efficacy than a single treatment when its component treatments have complementary, additive, or synergistic pharmacodynamic effects. Component treatments often generate better health outcomes when used in combination because they target different pathways or levels of a disease. These scenarios can and do occur in many different disease areas, however this Whitepaper will focus on combination treatments in oncology as a case study. This is due to the frequency of combinations of treatments in this disease area, where both components are branded (i.e., on patent) medicines. Furthermore, the Whitepaper and the proposed solution only consider patented or branded medicines. Generic medicines are not considered as there is likely more than one manufacturer of the generic treatments making any meaningful arbitration challenging.

An example of how component treatments can produce better outcomes in oncology can be found in the interaction between pertuzumab and trastuzumab. Both immunotherapy treatments, they each bind to different human epidermal growth factor receptor 2 (HER2) epitopes. Their combined use provides dual blockade of HER2 signalling pathways, which translates in practice into improved survival for patients with HER2-positive metastatic breast cancer [10]. Similarly, a combination treatment may generate better health outcomes because the activity of one component treatment increases the effect of the activity of another. In another example, research suggests that pembrolizumab, another immunotherapy treatment, may increase the effect of pemetrexed-platinum, a doublet chemotherapy, and thereby enhance antitumour activity when they are used in combination to treat programmed death-ligand 1 (PDL1) positive advanced or metastatic non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations [11].

2.2 Economic evaluation of combination treatments

In the UK, novel treatments and technologies are typically subject to rigorous health economic assessment to optimise the allocation of finite NHS healthcare resources.

Currently, HTA agencies evaluate combination treatments using the same methods used to evaluate single treatments and, in most cases, the original backbone treatment. Yet there are systemic factors that make it difficult for combination treatments to achieve cost-effectiveness and remain within the Willingness To Pay (WTP) thresholds when applying conventional cost-effectiveness analysis (CEA) methods.

A feature of combination treatments, that influences the results of CEAs, is that both component treatments are often patented novel treatments. Adding a potentially high-cost treatment to an already high-cost backbone treatment will increase drug acquisition costs significantly. Since all treatments are evaluated at the same WTP threshold, the combined costs of two or more patented treatments will often exceed the WTP even if the add-on treatment is given away for free.

Manufacturers only have control over the price of their own treatments and not the overall combination. The backbone treatment normally will already have gone through the appraisal process and have a set price, which may also include a patient access scheme (PAS) or a managed access agreement (MAA). Furthermore, the price of the existing backbone treatment may already be set close to the WTP for its associated health benefits, which leaves little room for the additional cost of the add-on treatment. This is the situation which led the NICE-commissioned DSU report to conclude that is it possible for a novel add-on treatment in a combination not to be cost-effective at zero price.

To illustrate this concept with cancer treatments, patients with cancer are commonly treated until disease progression occurs. Therefore, if a novel combination treatment (i.e., consisting of two or more treatments) delays disease progression, patients are consequently treated with the combination (including the backbone treatment) for a longer period [12,13]. The DSU showed that, even if the price of the add-on treatment equals zero, the longer duration of treatment with the backbone treatment increases its cost and that the cost of the backbone treatment alone may exceed the WTP threshold. This is the most frequent reason why novel cancer combination treatments fail to achieve cost-effectiveness.

2.3 Consequences of the problem

The potential consequences of the challenges of assessing and therefore funding combination treatments are wide-ranging and impact many stakeholders.

For patients and their families, a diagnosis of a serious, complex, debilitating and life-limiting disease can be a terrifying reality. Patients quickly need to come to terms with the situation, and important life-changing decisions need to be made about their treatment and care [14]. Often, patients and their families need to deal with the fact that there are no treatments available. This can be devastating news to receive, and incredibly challenging to process emotionally. However, what is often worse is to find out that effective and safe treatments exist but are not approved for use due to cost-effectiveness challenges.

This situation is also very difficult for researchers, clinicians and nurses who strive to offer the most clinically effective treatments to their patients and are aware of effective treatments but are unable to offer them to their NHS patients. HTA bodies and local health authorities such as the NHS, who strive to approve safe and effective treatments, are also impacted by this situation as they do not currently have the methods and frameworks to address combination treatments which may not be cost-effective at zero price [10]. In the 2019 Voluntary Scheme agreement, between the Association of the British Pharmaceutical Industry (ABPI), the UK Department of Health and Social Care (the Department), NHS England and other Scheme Members, the Department and NHS England recognised the challenges of

realising the full potential health benefits from branded combination treatments given the need for commercial confidentiality and competition law and supported industry efforts to explore legally compliant solutions [9].

The impact on the pharmaceutical industry is considerable. The issue of cost-effectiveness of a combination treatment can lead to safe and effective treatments not being launched or non-submissions for HTA where a manufacturer deems there is a very low possibility of achieving reimbursement. These delays and barriers to reimbursement can have a devastating and knock-on impact on stifling investment in research and development.

Taking these potential consequences together, the significance of the current problem is demonstrated. This challenge is expected to grow in magnitude as more combination treatments are developed in a growing number of disease areas. Unless solutions are developed, piloted and refined, the situation will get worse and continue to create significant, unsustainable and unacceptable consequences for all stakeholders, not least the patients in need.

2.4 Co-creation

A critical success factor in developing a solution that would be acceptable and implementable to all stakeholders (upstream and downstream) and decision-makers was to involve them in its design. There would be limited benefit in proposing a solution and framework that did not fit the needs and constraints of all stakeholders directly implicated in the development, assessment, reimbursement and prescribing of combination treatments, and not least those who stand to ultimately benefit from them: patients and their families.

With this in mind, Takeda established an independently chaired, multi-disciplinary Advisory Group consisting of experts in competition law, clinical practice, research, health economics and academia as well as patient advocacy. Furthermore, the Advisory Group received input from representatives from NICE and NHS England on the implementation requirements for a solution.

Throughout, the Advisory Group were aware of and worked closely with other groups who were also working on potential solutions in an open and transparent way, sharing knowledge and ideas. There was a strong belief that a viable solution would take multiple efforts, working on the challenge from different angles and perspectives.

The objective of the project and the challenge for the Advisory Group was to develop a proposed solution which: would be transactable and implementable; complied with existing HTA methods and processes; legal and manufacturer regulations; and ultimately would enable a path for licensed combination treatments which demonstrated clinical value to become available to patients.

The main issues to be addressed by any potential solution are described in **Section 3: Requirements for a solution.**

3. Requirements for a solution

There are many distinct issues that arise when assessing the value of combination treatments. While the NICE 2014 DSU paper described the HTA challenges in appraising combination treatments (further explored in the sister Whitepaper[7]), significant operational issues exist that would need to be addressed with any proposed Framework [5].

In order to develop a solution to this complex problem, the Advisory Group first identified the main issues and considerations that would need to be addressed for any proposed solution to work. The creation and design of the conceptual Arbitration Framework and SOP was developed to specifically meet the unique and complex needs of the ecosystem around the appraisal of combination treatments [7].

Following a robust assessment of the current HTA landscape, competition law and stakeholder needs, the Advisory Group identified the main requirements [4]. These are outlined in **Figure 1** and further described below.

Figure 1: Requirements for a voluntary Arbitration Framework

3.1 Must be compatible with existing HTA methods and processes

A requirement from NICE and NHS England was that any proposed solution should fit within or alongside the existing methods, processes, and timelines for an HTA appraisal; there was no scope to change these or introduce steps which would delay a NICE appraisal outcome. Working alongside the Advisory Group, the proposed arbitration process and SOP was built around these requirements.

A simplified diagram of the Arbitration Framework and SOP was mapped out alongside the NICE appraisal process to demonstrate alignment and touch points, and to give an indication of timelines. Accompanying text was also drafted to expand on each stage of the Framework to illustrate the requirements and responsibilities at each point. This is presented in **Figure *2***.

3.2 Must adhere to existing cost-effectiveness thresholds

As well as adhering to existing HTA and commissioning methods (specifically NICE and NHS England in this proposed Framework), processes and timelines, a requirement of any viable solution was that to be deemed cost-effective, the combination treatment must still meet the current WTP thresholds.

This was a conclusion of the Bellberry Group whereby international HTA bodies concluded that raising the WTP threshold was not possible or justified [4]. If funded, the local health system, i.e., NHS England in the context of this Whitepaper, would pay for the costs of the combination treatment in totality. This would displace other health resources in the context of a fixed budget system, regardless of if the treatment was a monotherapy or a combination. Representatives from NICE and NHS England, from whom the Advisory Group received input, agreed with the Bellberry Group conclusion; that there was no scope to change the current WTP threshold.

Therefore, any proposed framework must adhere to existing rules on cost-effectiveness analysis, yield a cost-effective combination under the existing WTP thresholds, and be compatible with current NICE methods and processes. How the WTP threshold is allocated among components of the combination treatment is explored in the sister Whitepaper.

3.3 Must address competition hurdles on exchange of price sensitive information

Special attention must be given to the requirements and regulations with respect to competition law for any proposed solution to be implementable and compliant; and this was a major consideration for the Advisory Panel.

UK competition law, enforced by the Competition Markets Authority (CMA) prevents individual manufacturers agreeing prices for their treatments as part of an agreement for splitting revenues from combination treatments, where this has the effect of also impacting prices for the treatments when sold on a standalone basis [15]. It also prohibits the exchange of pricing or other sensitive commercial information that could have the effect of limiting competition between the manufacturers when supplying their treatments on a standalone basis [16]. Mechanisms are therefore required to ensure lawful discussions. These mechanisms will also need to satisfy the internal compliance rules of manufacturers.

Individual manufacturers encounter challenges in dialogue with other manufacturers due to their need to comply with competition law. However, over, and above mandatory compliance with competition law, different manufacturers have further layers of internal processes and compliance requirements which need to be considered. These internal compliance requirements may be set at local, regional, and international levels, and vary between manufacturers. The internal restrictions may further amplify the prohibitions imposed by competition law and restrict interaction with other manufacturers. Misaligned incentives, particularly given the potential revenue downside which the backbone treatment manufacturer may expect to have to bear, and the need for price confidentiality must be addressed to enable intercompany dialogue. This is due to the probability that manufacturers are likely competitors in settings outside of the combination treatment.

The requirements stipulated by competition law and the further internal requirements from individual manufacturers must be met, as failing to meet either in a proposed framework would render the framework unimplementable.

3.4 Must encourage and incentivise manufacturers to work together: non-uniform pricing

3.4.1 Legal considerations of non-uniform pricing

In the UK, a single uniform price for treatments across all indications is the standard expectation from the NHS payer, in this case NHS England. The 2019 Voluntary Scheme between the ABPI and Department of Health states that the health service in England adopts uniform pricing and it does not adopt blended or indication specific pricing – setting a different price for each major indication approved for a treatment, with different prices across indications reflecting different values [9].

Furthermore, the Commercial Framework published by NHS England in 2021, reinforces that simple discounts and uniform pricing are the default and other commercial arrangements are only available in exceptional circumstances, on a case-by-case basis [17]. Both the Voluntary Scheme and the NHS Commercial Framework however state that "in cases where uniform pricing would lead to a reduction in total revenue for a medicine overall from the introduction of additional indication, other forms of commercial flexibility may be considered for medicines with a strong value proposition." [9,18] Encouragingly, the NHS Commercial Framework recognises that due to the competition and commercial challenges, branded combination treatments may require bespoke solutions [18].

The Authors recognise and support Principle 3 of the NHS Commercial Framework which states that commercial arrangements should consider and minimise the burden on the NHS and frontline staff and be transactable [18]. However, given the challenges presented by combination treatments presented throughout this paper, the Authors believe that circumstances around combination treatments are exceptional and warrant consideration for non-uniform pricing.

The lack of non-uniform pricing is a challenge to the cooperation of the backbone manufacturer and, critically, a key reason for the aforementioned competition law problem. A lack of price flexibility means that the prices agreed for the combination treatment automatically apply to all other indications of the combination components when sold as standalone treatments or within other combinations. If only uniform pricing was allowed, any discussion of the combination treatment discounts would result in agreeing on the discounts for the standalone treatments and all other uses of the backbone treatment as well. The standalone treatments may be competitors in other indications or lines of treatments, and therefore agreement on discounts or net prices for the current combination treatment may also amount to an agreement between the manufacturers on prices in indications where the component treatments are in fact competitors. This may be seen as price fixing and would likely contravene UK competition law.

> *For example, Treatment A may be used as a monotherapy for breast cancer and prostate cancer. Treatment B may also be utilised as monotherapy for breast cancer. The manufacturer of Treatment B may now wish to bring Treatment B in a combination with Treatment A for the treatment of prostate cancer. Irrespective of whether Treatments A or B are used in breast cancer or prostate cancer, all the prices are uniform under current NHS England guidance – the net prices are exactly the same (including any confidential discounts that have been implemented). Therefore, if the manufacturer of Treatment B were to find out the confidential price of Treatment A in the combination, they could also utilise that information to adjust their pricing in all other combinations and indications.*

Allowing combination specific non-uniform pricing will, as a result, be critical to avoiding any breach of competition law when agreeing on the component prices for the combination. It will also be critical to incentivise manufacturers to enter in meaningful discussions and any potential agreement as it could

be limited to the combination treatments in that setting only and would not risk either manufacturer's business outside the combination. This is further explored in the section below.

3.4.2 Commercial considerations of non-uniform pricing

Even if a mechanism of inter-manufacturer dialogue which doesn't breach competition law or internal requirements is established, consideration must be given to the incentives and commercial impact of any agreement on the backbone manufacturer. If only uniform pricing is available, any discounts agreed for the component treatments as a part of a combination commercial agreement would have a detrimental impact on the entirety of the revenues of the backbone treatment. In this situation, the backbone manufacturer may 'lose out', while the add-on manufacturer may stand to 'gain'. It is likely that the situation will result in one 'driver' (manufacturer who stands to gain) and one 'passenger' company (manufacturer who stands to lose).

Resistance to participation from the backbone or 'passenger' manufacturer, locally and globally, is expected if the agreement on the combination impacts business and revenues for the backbone treatment in this or other settings. Enabling non-uniform pricing specific to a commercial arrangement for the combination would not have a commercial impact on the backbone treatment's other indications. The Authors believe this is critical to bringing both parties to the arbitration table. This is essential in ensuring the 'passenger' company that manufactures the backbone treatment is a willing participant who engages in any intercompany dialogue.

Furthermore, any proposed framework needs to be long-term in nature; any given manufacturer is likely to be both a driver and a passenger at different points in time. A long-term agreement from manufacturers to take part in an agreed process would work to incentivise and encourage participation as, over time, individual manufacturers would benefit from such a process being available. Even if it is not in an individual manufacturer's short-term commercial interest to participate in a combination agreement today, they may be the 'driver' in a future appraisal and would stand to benefit from the process.

3.5 Must agree to a common value attribution methodology

To enable productive inter-company dialogue, there is a need for a mutually accepted, and preferably industry-accepted methodology of understanding the proportion of the contribution of both the backbone and add-on treatment to the combination. Negotiations are likely to fail if manufacturers are unable to agree on a common framework which allows 'value' to be assigned to each combination component. Therefore, a common value attribution methodology is required, which can act as a starting point of negotiation between the two manufacturers. This critical part of the solution is addressed by the sister Whitepaper, *An Attribution of Value Framework for Combination Therapies* [7].

4. Description of voluntary Arbitration Framework

The above sections have (i) described the problems that the Framework needs to solve, and (ii) the resultant core requirements of the Framework. After extensive discussions with the Advisory Group and input from experts from NHS England and NICE, the proposed Framework set out in this section is one which the Authors believe can enable manufacturers to legally engage in inter-company dialogue.

This section sets out: (i) The key components of the solution, which meet the requirements identified. (ii) A high-level summary of how the Framework will operate.

A step-by-step diagram and description of the Framework in detail is presented in Figure 2 and in Section 4.2 below.

4.1 Key components

To meet the aforementioned requirements effectively, the development of novel approaches is needed. The requirement for a common value attribution methodology, for example, is addressed by the new approach outlined in the sister Whitepaper. However, the requirements to (i) be compatible with existing HTA and commissioning methods, processes, and policies and (ii) adhere to existing cost-effectiveness thresholds are fundamental and are embedded in the Framework's design.

The requirements to address competition law hurdles and encourage manufacturers to work together in particular require some new processes:

4.1.1 Clean teams

The Framework's proposed solution to address the competition law issues described above would be to utilise 'clean teams' for the purpose of sharing and receiving confidential information. Setting up clean teams would ring-fence the information divulged and received and work to avoid the dissemination of sensitive data to the wider businesses [19].

- Clean teams are used in merger-and-acquisition transactions to manage information sharing between merging businesses. Companies that are planning a merger need to share information to negotiate regulatory approval for the transaction [18]. At the same time, however, there is a risk that if the deal does not complete, the sharing of this commercially confidential information will undermine future competition between the two businesses.

- The solution to this problem is the use of clean teams which are separate from the operational management of each company. These teams carry out data collection and analysis, and if the deal does not complete, will not be in a position to use the information that they have had access to in the management of their company.

- The clean team on each side, which would be responsible for negotiating the agreement between the manufacturers, would not be involved in the day to day strategic or commercial management of the component treatments. This would address the risk that commercially confidential information held by employees involved in the strategic or commercial management of each component treatment was shared (inadvertently or otherwise) with the other manufacturer during the negotiation process.

- The clean team would operate under a mandate from the management of each manufacturer and its responsibilities would end once an agreement was reached. The terms of the agreement would be shared with both parties. That is, both manufacturers of the combination components would know the discount from its public list price that the other party has agreed as part of the combination therapy. However, the discount that each party has agreed with the NHS for the standalone treatment outside of the combination treatment would remain confidential and would not have to be shared as part of this negotiation process.

- Clean teams, when used by merging or acquiring businesses, may comprise both company employees and external consultants. A clean team would need to comprise of appropriate representatives of each company involved in the combination treatment, who could enter discussions but would not be involved in the development, pricing, or marketing of either standalone treatment approved for reimbursement or other treatments where the manufacturers are competitors. However, an internal clean team may not be appropriate in this setting as described below.

    - Clean team members must be both familiar with the process of HTA and the combination treatment appraisal specifics, however, they must also be removed enough from the business to ensure the information exchanged during the arbitration is ring-fenced. Unlike a merger and acquisition transaction where employees from local affiliates who do not work in the specific business unit may be far-enough removed to take part in a clean team, it is unlikely that any internal employees who are capable of leading a discussion on a specific combination treatment's HTA process will be far-removed from the business impacted. Therefore, for the purposes of any inter-manufacturer dialogue or arbitration for combination treatments, it is recommended that manufacturers fully externalise their clean teams and hire third-party agencies operating under contracted mandates to represent them. This will provide additional security by ensuring that no company employee is privy to sensitive pricing information from their clean team counterparts.

4.1.2 Use of non-uniform pricing

The Authors recognise that in the UK, the default commercial arrangements must be simple and with uniform pricing. Both the NHS Commercial Framework and Voluntary Scheme agreement reinforce that simple discounts and uniform pricing are the default and other commercial arrangements are only available in exceptional circumstances, on a case-by-case basis [9,17]. However, due to the unique challenge presented by combination treatments described in Section 3.4 above, the Authors argue that combination treatments require allowance of non-uniform pricing.

Therefore, the proposed Voluntary Arbitration Framework assumes that payers will allow non-uniform pricing for the component treatments. This bespoke arrangement unique for the combination would not impact any prior backbone discount agreement, nor would it impact future indications of the add-on treatment. Without the allowance of non-uniform pricing, specific to the combination, the backbone manufacturer would be unlikely to engage in discussions as there would be commercial risk to the rest of the business. The Authors believe this scenario, loss of revenue for the backbone manufacturer due to the introduction of the combination, meets the conditions of clause 98 of the NHS Commercial Framework:

> *"In cases where uniform pricing would reduce the total revenue for a medicine from introducing additional indications, other forms of commercial flexibility may be considered for medicines that have a strong value proposition."* [16]

Furthermore, if non-uniform pricing was not available, any commercial discussions between manufacturers on the components for this combination may be a breach in competition law, as the agreed commercial arrangement for each component would apply uniformly to all its indications, including where the treatments may be competitors.

The development of the Framework has also incorporated the input from experts from NHS England and the Authors would therefore like to emphasise that this solution is unique and exclusively proposed for combination treatments which are not able to reach a viable arrangement without this bespoke solution. The Authors believe that the option of non-uniform pricing specific for the combination can be ring-fenced to only treatments that qualify for the Voluntary Arbitration Framework

The Authors would like to emphasise the need to ensure transactability of commercial arrangements, including for those reached through the Voluntary Arbitration Framework for combination treatments. Due consideration from all parties, including the manufacturers, clean teams, and the Arbitrator, must be given to minimise burden on the NHS and NHS frontline staff – this extends to the use of non-uniform pricing for combinations. Further work is needed with industry and NHS England to agree a mechanism to transact a combination specific arrangement on the principle of simplicity, minimising burden on the NHS and frontline staff.

4.1.3 Long-term commitment from all participants to partake in the voluntary arbitration process

Any proposed process or framework will require buy-in from all manufacturers, NHS England, NICE and the industry body (The Association of the British Pharmaceutical Industry – ABPI). The Authors propose that the voluntary arbitration process should be included in the next VPAS agreement and request commitment from individual manufacturers to engage in the process with no obligation to be bound by any outcomes.

The Framework is built on the foundation that manufacturers will commit to the following principles:

- Each manufacturer will use best endeavours to make combination treatments available to patients.

- Each manufacturer will work with other manufacturers to arrive at combination-specific discounts which are plausibly cost-effective.

- Each manufacturer accepts that combination treatments will be assessed in line with standard NICE cost-effectiveness thresholds and NHS England's budget impact test. Furthermore, that each component treatment of the combination will be evaluated in line with an agreed methodology.

- Each manufacturer accepts that this process is only applicable to combination treatments.

- Each manufacturer agrees to follow the Voluntary Arbitration as overseen by an independent arbitrator (see below) – and in good faith partakes in the process. However, each manufacturer can walk away from the process should an agreement fail to be made. Under this proposal, manufacturers would commit to participate in the process with good faith but reserve the right to leave the arbitration at any point.

4.1.4 Role of the Arbitrator

The Framework envisages the appointment of an independent arbitrator or mediator, the Arbitrator, to facilitate the discussion. The Arbitrator will have three important functions:

- Determining which combination treatments meet the criteria for requiring the use of the Voluntary Arbitration Framework. This is to ensure that the Framework is used in those limited cases where demonstrating cost-effectiveness for the combination treatment is challenging through existing processes.

- Facilitating and chairing dialogue between manufacturers throughout the process and communicating progress to the payer (i.e., NHS England) when required.

- Acting as arbitrator or mediator on value attribution disputes. The sister Whitepaper sets out a value attribution process which is meant to act as the starting point for discussions on the value contributed by each component, expressed in terms of Quality-Adjusted Life Years (QALYs), the NICE preferred unit of value. However, the output of the value attribution method is the starting point and different interpretations of value from each manufacturer are likely. Agreeing on an appropriate allocation of the QALYs to each component is the main topic of the discussions guided by this Framework. To ensure disputes on attribution do not stall the process, the Authors believe there is a case for independent arbitration.

We see the Arbitrator having an important role to play in the overall success of the Framework, by using their expertise to help facilitate negotiations between the manufacturers. The pharmaceutical industry in the UK already has experience of voluntarily submitting to third party authority (the Prescription Medicines Code of Practice Authority – PMCPA) for the purposes of regulating the ABPI Code of Practice. The Authors therefore see the more limited role of the Arbitrator to be a viable and practicable concept in this case.

4.2 High-level summary of the Voluntary Arbitration Framework

The Framework has six phases, with the specific steps under each phase:

- In Phase 1, the manufacturer of the add-on treatment will signal the existence of a possible combination treatment issue via existing horizon scanning during the National Institute for Health Research Innovation Observatory (NIHRIO) briefing stage, or scoping stage of the NICE process. The Arbitrator would then decide whether to engage the Framework, according to certain criteria – which may include whether both treatments are on-patent and if both manufacturers are committed to the Framework.

- In Phase 2, the value attribution process – described in the sister Whitepaper – is run, with manufacturers submitting information to determine which proportion of the value, expressed as the proportion of the incremental QALY, the backbone and add-on treatments provide. In this phase, the manufacturers hire external bodies to form their clean teams and begin to negotiate the proportion of value attributed to each component based on the starting point set by the outcome of the value attribution process. In case of dispute over the value attribution result, the Arbitrator may arbitrate. The Authors envisage this phase taking place after the NICE scoping stage; however, a revisit of any agreed allocation is likely required after the NICE Committee preferred assumptions and the corresponding incremental QALY is available. This is likely only

available after the Technical Engagement stage or the first NICE Appraisal Committee Meeting (ACM).

Although not necessary, a representative of NHS England will have the option to attend the Voluntary Arbitration meetings as an observer only; the Arbitrator would have sole responsibility for facilitating Voluntary Arbitration meeting(s). For clarity, the Authors propose that the manufacturers negotiate the proportion of the QALY attribution and the corresponding percentage of the WTP threshold. Following this outcome, each manufacturer would set a corresponding discount to match this value. The discount agreement or patient access scheme (PAS) for each treatment remains to be an agreement and transaction between NHS England and each individual manufacturer directly.

- In Phase 3, NICE conducts an appraisal of the combination treatment. The clean teams may reconvene following the Technical Engagement stage and the first ACM to explore how their agreement in principle needs to change to reflect the NICE Committee's preferred assumptions and the respective QALY gain and ICER. If Phase 3 results in a positive Final Appraisal Determination (FAD), then phase 4 of the framework is bypassed. Any adjustment to the mutually agreed value attribution to each component based on the outcome of Technical Engagement on the plausible QALY and incremental cost-effectiveness ratio (ICER) may require manufacturers to re-engage with NHS England on the previously agreed PAS, if needed.

- In Phase 4, and in the event of the NICE Committee issuing a negative Appraisal Consultation Document (ACD), the clean teams are reconvened for discussions with the objective of reaching an agreement whereby the combination treatment is cost-effective under the expected final assumptions. This meeting would be facilitated by the Arbitrator and following an agreement in principle, each manufacturer would be required to finalise a commercial agreement directly with NHS England, reflecting the agreed-upon valuation. It is proposed this phase will have a time limit consistent with an ACD response, of four weeks, which would ensure neither side unduly delays the negotiations nor impacts existing NICE timelines.

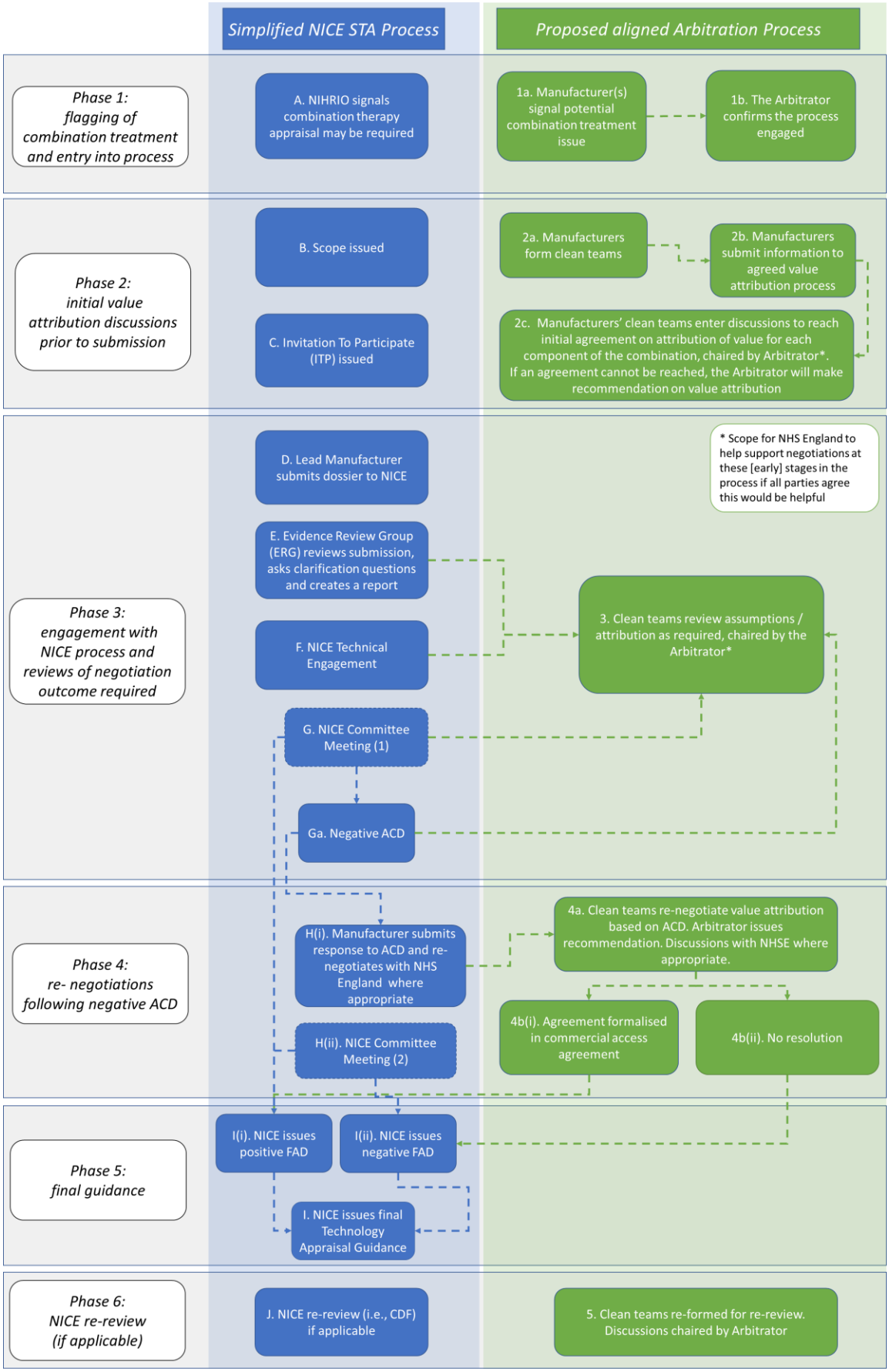
- In Phase 5, if the combination treatment is found to be cost-effective, NICE would issue a FAD based on the combination specific commercial access agreement agreed with NHS England.

- In Phase 6, NICE may re-review its guidance, either in line with its usual processes or in line with the commercial access agreement negotiated in phase 4.

The Authors of the Framework would encourage goodwill from both the backbone and add-on manufacturers to take part in the process and urge best efforts be made to agree a negotiated deal. However, it is recognised that this may not always be possible. Therefore, a key to the Framework is that the process is purely voluntary, and any outcome would not be binding and could not be imposed; each manufacturer has discretion to terminate the arbitration.

The Arbitrator would provide a transparent and clear process for dialogue between combination manufacturer companies. There would still, however, be necessary pricing discussions with the final NHS payer – in this case NHS England.

Figure 2: Proposed Voluntary Arbitration Framework process map



5. Discussion and key questions

Takeda, in collaboration with the Advisory Group, set out to propose a solution to a long-standing issue – combination treatments – one that has prevented, for various reasons, access for patients to many safe and effective combination treatments. This proposed solution is a starting point for discussion and the Authors hope to generate dialogue, to get feedback on the proposed solutions and to stimulate further thinking to ultimately help define a solution to this issue which can be adopted by all stakeholders.

To the knowledge of the Authors, the proposed solution, described over the two sister Whitepapers, is the first comprehensive proposed solution covering both the economic value attribution challenge and a practical framework for outlining how inter-company discussions could be conducted in a compliant manner. By taking the approach to develop a solution from the ground up, the Authors hoped to have a proposal which is implementable and transactable.

The proposed solution described in this Whitepaper was built on a thorough diagnosis and understanding of the issues and restrictions each affected party faced. The Framework was developed with the aim of mitigating these issues; each proposed element of the Voluntary Arbitration Framework works to address an identified issue in a complementary manner. A key strength of the proposed solution is that it was co-created by multiple stakeholders, all who have different needs and perspectives, so that the proposed Framework is acceptable by the key parties.

The Authors primarily looked at the issue through a UK lens, specifically England. However, recognising that this is an international issue, it was important that any solutions could be adapted relatively easily to fit other markets and jurisdictions which use cost-effectiveness assessments for decision-making. Although there is heterogeneity between the processes and methods among HTA bodies, and between competition law and pricing mechanisms in different geographies, the underlying principles are similar. Therefore, the principles and building blocks of the proposed solution should be adaptable internationally, with modifications applied to suit a specific country's individual mechanisms, processes, and requirements, as needed.

Although the Authors have strived to create a proposed solution which addresses the multifaceted issue of combination treatments, and took care to propose frameworks which are compliant, acceptable, and implementable, there are still outstanding challenges and limitations of the proposed Value Attribution framework.

Firstly, does the proposed Value Attribution framework go far enough to incentivise the backbone company or 'the passenger' to participate in the process? The framework proposes acceptance of non-uniform pricing for the combination that won't impact the rest of the backbone manufacturer's business outside of the combination. Furthermore, the proposal to include a long-term commitment to participate in the Voluntary Arbitration Framework via the VPAS agreement (or a similar process) should ensure that over time the impact on manufacturers balances out. Backbone companies will be add-on companies at some point and would benefit from having an agreed process available.

However, will this be enough to incentivise the backbone manufacturer to participate? Inclusion of a clause within the next VPAS agreement asking manufacturers to commit to participate is proposed. The VPAS agreement was recommended as it an agreement which already exists and has broad membership among industry. However, it does not include all manufacturers and is already a complex agreement requiring the buy-in from multiple stakeholders. Is the VPAS the most appropriate

agreement in which to include commitment to participate? Is there another option to ensure this is adopted by industry and authorities?

What if there are multiple combinations with the same backbone treatment? How do we protect backbone manufacturers from agreeing to a combination treatment deal with add-on treatment A but not with a future add-on treatment B? This may lead to backbone manufacturers being accused of 'excluding' some combinations from the market and therefore behaving anti-competitively. The Authors believe that through the commitment of the backbone manufacturer to come to the discussion table and make best efforts to reach an agreement, the manufacturer would not be in breach of competition law, even if an agreement is not reached. Furthermore, by allowing for non-uniform pricing for use of the component treatments in the combination, the backbone manufacturer would be able to make an independent business decision on the proposed combination with treatment B, independent from other agreements and any existing standalone discounts. However, the administrative implications of the introduction of non-uniform pricing on the NHS need to be considered. Further work is required to define a mechanism to implement non-uniform pricing for the combination which is transactable and minimises burden on the NHS.

Concerns around competition law and any potential or perceived breaches were at the forefront of the creation of the proposed Voluntary Arbitration Framework. The balance of adding complexity and ensuring compliance is challenging. However, the Authors' proposal of utilising external clean teams to act on behalf of manufacturers to partake in the intercompany dialogue works to address this issue. Nonetheless, uncertainties remain; are clean teams a viable option? To ensure compliance and acceptability from internal legal teams, the current framework proposes external consultancies to act as clean teams. Could internal teams, who are still far enough removed, act as clean teams to avoid additional bureaucracy and costs? The cost of external clean teams may be prohibitive for smaller manufacturers. Furthermore, the risk appetite for different manufacturers varies: would the idea of clean teams be acceptable to conservative manufacturers, global head office teams and competition authorities? Does the proposed Voluntary Arbitration Framework address the competition law requirements or are there outstanding challenges which have not been considered?

The Voluntary Arbitration Framework proposes the building blocks of a potential Framework, but more work is needed to define granular requirements – such as which information would be shared among the clean teams. Under the proposal, manufacturers and their clean teams would discuss and agree on the incremental QALY and ICER split. However, the commercial access agreement, or PAS, is made directly with NHS England and each manufacturer. Is there a need for a 'terms of engagement' or confidentiality agreement to be signed between the two manufacturers?

The role of the Arbitrator under the current proposal would be to facilitate the Voluntary Arbitration process and mediate any disagreements between the manufacturers on the value attribution. Furthermore, having an independent party would add reassurance that the proceedings are compliant with competition law. The Whitepaper envisions this role to be akin to an existing industry body, the PMCPA, who operate independently to settle disputes among industry members. However further work is needed to define what qualifications this role would require, whom they would report to, and how their resourcing would be secured.

In addition, what are the responsibilities and powers of the Arbitrator – are they more aligned to a mediator or an arbitrator? What is their relationship with NHS England and NICE? The Authors recognise that establishing an independent arbitrator may introduce additional intricacies that requires investment, however they felt it was needed for a compliant and transparent process.

The Authors approached the design of the proposed Voluntary Arbitration Framework to work alongside the existing NICE processes and timelines with the aim of avoiding any delays to the outcome of the appraisal and access to treatments. The proposed Framework envisions that the majority of the value attribution and the corresponding arbitration will occur prior to the NICE submission by the add-on treatment manufacturer. But will sufficient information be available before submission to allow for a meaningful discussion on the likely value of the combination (i.e., incremental QALYs) and its attribution to component treatments? In existing HTA appraisals, it is common for the assumptions which yield the NICE Committee preferred incremental QALYs and ICER to change throughout the process. If the assumptions drastically change between submission and committee meeting resulting in a draft negative recommendation, is one month (as currently allowed for an ACD response) sufficient for a full re-negotiation? Although the aim of the proposed Voluntary Arbitration Framework was to adhere to the existing timelines, flexibility may be required to accommodate discussions between combination manufacturers.

The proposed Framework focuses on the operationalisation to enable inter-manufacturer dialogue, but further consideration for longevity of any agreement is needed. What is the impact on any combination-specific discount or agreement should a backbone or add-on treatment become generic? Likewise, if the combination is recommended for the Cancer Drugs Fund (CDF) and will require a reappraisal? Potential solutions could be either fixed-duration agreements that expire at loss of exclusivity (LOE), or re-negotiation at exit from CDF with the committee preferred QALYs and ICERs based on the final data used for the post-CDF reappraisal. In short, more consideration is needed to ensure the framework is future-proof.

6. Summary and next steps

This Whitepaper started by describing the challenges of demonstrating cost-effectiveness and reimbursement for combination treatments and represented the impact of this issue on the key stakeholders. This was followed by an overview of the approach Takeda took to establish an Advisory Group of key stakeholders who were invited to explore the existing issues and requirements, and based on those, co-create a potential solution. We received input from NHS England and NICE to understand their requirements and acceptable parameters of any potential solution.

This Whitepaper then went on to present the second part of the outcome from this work, a proposed Voluntary Arbitration Framework which would enable manufacturers to take part in compliant inter-manufacturer dialogue. The first part, the economic attribution of the combination's value, has been presented and discussed in a sister Whitepaper named *An Attribution of Value Framework for Combination Therapies* [7].

Jointly the two Whitepapers propose a comprehensive solution to the issue of combination treatments. However, the Authors note that these frameworks are only proposals whose intention is to stimulate discussion, dialogue, and feedback. This is a starting point which likely requires further refinement.

Takeda and the Authors are aware of other stakeholders and groups who are also working to develop solutions to the issue of combination treatments. The Authors welcome all work on this complex issue and believe that every proposed solution adds to the discussion and will bring the community closer to ultimately solving this important issue and hopefully enabling access to important combination treatments for the patients who need them.

Having read and reviewed the proposed solution, the readers may agree that there are outstanding questions to ask and debate. The Authors would therefore encourage all interested parties to think about the proposed Voluntary Arbitration Framework, the outlined limitations and invite the readers to engage and feedback on both Whitepapers via the following email: combinationmedicinesUK@takeda.com

Appendices

Standard Operating Procedure

The table below describes each step of the new voluntary arbitration process (summarised in the diagram appended) in more detail. Each description is accompanied by a summary of the issues considered in the development of the Framework. Note that the alphabetical steps correspond to the existing NICE process and numerical steps correspond to the voluntary arbitration process.

Description	Considerations
Phase 1: flagging of combination treatment issue and entry into the process	
Step A. NIHRIO signals potential combination treatment appraisal	
Through the current horizon scanning, NIHRIO will identify combination treatments which are likely to be appraised by NICE. Should an HTA be required, NIHRIO will forward this notification to NICE, inform the manufacturers and may inform the Arbitrator.	The Authors are seeking to identify an early but robust point at which all parties can be given fair warning of a potential combination treatment issue. It is proposed that the initial filtering process occur at the NIHRIO briefing stage.
1. Company/ies signal potential combination medicine issue	
As an alternative to NIHRIO's signal, the manufacturer(s) may also cite the Arbitrator on the combination treatment in question.	Although the NIHRIO signal in Step A is the 'formal' point of identification for a combination treatment issue to NICE and the Arbitrator, it is valuable to offer manufacturers an earlier opportunity to signal this issue, if possible, so that the process can begin as early as possible.
1b. Arbitrator confirms process engaged	
The Arbitrator will review the signal from NIHRIO or from the manufacturers against a set of criteria for entry to the process, and then take a final decision over whether to engage the process.	Certain criteria for entry should be identified and met for the process to be engaged in order to avoid its overuse. These criteria might include (for example) ensuring that all treatments entering the process are on-patent, and that the treatments meet certain standards of innovation. However, the criteria would be developed in discussion between the NHS and industry. It is proposed the Arbitrator take the final decision as to whether treatments should enter the process.
Phase 2: value attribution and initial intercompany discussions during scoping	
Step B. Draft scope issued	
At this phase, NICE has issued the draft scope for its appraisal of a combination treatment.	n/a

2a. Manufacturers form clean teams	
Once the process has been formally engaged, manufacturers will form their 'clean teams' (proposed external personnel) for the purposes of the negotiation. It is proposed initial negotiations commence as soon as manufacturers and their respective clean teams are ready.	The proposed Framework requires clean teams to be formed once the process has been formally engaged. In order to minimise risk of competition law breach, it is proposed clean teams be outsourced to an external party. Further guidance will need to be developed on how clean teams should be constituted (functions and areas of expertise). The Authors propose that this guidance will set out the overall principles that manufacturers should adhere to in establishing and operating a clean team. It could also usefully include some illustrative examples that demonstrate how these principles could, in practice, be met. The Authors propose the guidance should also set out overall principles and objectives rather than prescriptive rules. It is important this guidance be developed in collaboration with internal legal teams and validated by external experts in competition law. This will provide manufacturers with comfort that adhering to the guidance on establishing and operating a clean team will give them maximum protection from any breach of competition law.
2b. Manufacturers submit information to agreed value attribution process	
Following the finalisation of the scope, after the process has been engaged, manufacturers will submit their initial evidence to the proposed Value Attribution methodology.	It is proposed the Value Attribution methodology, as described in the sister Whitepaper, be used to calculate the proportion of the incremental QALY gain attributed to each component treatment. This 'proportional attribution' will serve as the starting point of negotiations between the clean teams.
2c. Manufacturers' clean teams enter discussions to reach initial agreement on attribution of value for each component of the combination, chaired by Arbitrator	
If manufacturers disagree on the outcome of the value attribution process, they can appeal to the Arbitrator. The Arbitrator will facilitate further dialogue and issue a recommended value attribution.	In order to avoid the value attribution process compromising NICE's Single Technology Appraisal (STA) process, it is recommended the Arbitrator issue a recommended value attribution at this early stage.
Step C. Invitation to participate (ITP) issued	

The Invitation to Participate starts the clock on the STA of the combination treatment NICE appraisal. The deadline to submit is 60 days from the ITP.	During this phase, assumption for the NICE submission will be refined by the submitting manufacturer (add-on treatment). This may require further negotiations with clean teams to agree on the appropriate value attribution and the respective QALY gain.
2d. Manufacturers' clean teams agree value attribution to each treatment via discussion facilitated by the Arbitrator. Manufacturers individually submit corresponding commercial agreements with NHS England.	
Following the ITP, manufacturers' clean teams will settle on the [initial] percent attribution of the incremental QALY gain for the combination treatment. The discussions will be facilitated by the Arbitrator. The respective manufacturers will individually agree matching net prices (corresponding to the QALY attribution) with NICE's commercial liaison team.	As stated above, in order to avoid risks under competition law, the input values from each manufacturer will be combination – specific. In order to align with existing processes, NICE's commercial liaison team will need agree to any commercial arrangement required base on the output of the negotiations with each manufacturer.
Phase 3: engagement with NICE process and reviews of negotiation outcome as required	
Step D. NICE commences review	
NICE conducts the STA of the combination treatment following the standard procedure and timelines. The submission is led by the add-on manufacturer.	It is proposed the add-on manufacturer (lead) will lead the NICE submission process and engage in all required steps of the STA process. Both clean teams should be informed of any material changes that occur throughout this phase.
Step E. Evidence Review Group report	
As now, the Evidence Review Group (ERG) will report on the lead manufacturer's submission. Applicable sections of this will be shared with all manufacturers' clean teams engaged in the process.	The ERG report will be the first point at which the assumptions underpinning the cost-effectiveness of the combination treatment (including the incremental value, QALYs) are accepted or challenged. As this may lead to material changes in the expected incremental value, it is likely required for the clean team to re-engage in negotiations.
3a. Clean teams review assumptions / value attribution as required, chaired by Arbitrator	

Based on the outputs of the ERG report, the clean teams may need to review the value attribution outcome, and if necessary, re-negotiate the proportional attribution to each component. Once again, these discussions will be facilitated by the Arbitrator who may issue a recommendation in the event of an impasse.	The ERG report is the first point at which manufacturers are likely to need to review their initial assumptions.
Step F. NICE Technical Engagement	
The NICE technical engagement step will proceed as an opportunity for manufacturers and consultees to provide responses to the ERG report and the main issues / uncertainties in the appraisal.	This is a key step in the process whereby the main issues in the appraisal are identified and may be resolved. Material changes to the expected incremental value (QALYs and corresponding ICERs) and relevant information submitted through the technical engagement step should be available to both clean teams.
3b. Clean teams review assumptions / value attribution as required, chaired by Arbitrator	
If the NICE technical engagement step results in material changes to the plausible incremental QALYs gain and the combination treatment ICER, the clean teams will re-convene to review their assumptions and the attribution once again. These discussions will be chaired by the Arbitrator.	Should the technical engagement stage result in a significantly different cost-effectiveness output (ICER) and therefore incremental QALY gain, it will impact the apportioned value to each component. If required, manufacturers may re-engage with NICE's commercial liaison team.
Step G. NICE Committee Meeting *Step Ga. Negative ACD*	
In the event that the NICE Committee is unable to conclude if the combination treatment is a cost-effective use of NHS resources following the first meeting, it will issue a negative ACD as now. If NICE is able to conclude that the combination treatment is a cost-effective use of NHS resources, it will proceed to step H(i) (a positive FAD, set out below).	This is the first view of the NICE Appraisal Committee's preferred assumptions and may result in material changes to the incremental QALYs and the Committee preferred ICER. A revisit of the Value Attribution may be required.

Phase 4: Clean team re-negotiations following negative ACD[1]	
4a. Clean teams re-negotiate value attribution based on ACD. Arbitrator issues recommendation. Discussions with NHSE where appropriate.	
In the event of a negative ACD, clean teams will need to re-negotiate based on the updated assumptions and the corresponding incremental QALY gain and ICERs. In the event of a dispute or failure to agree, the Arbitrator will issue a recommendation on the preferred attribution. Any agreed change in value attribution of either component may require a corresponding discount adjustment. Each manufacturer will engage directly with NHS England NICE's commercial liaison to effect these changes. Based on the complexity of combination treatment appraisals, it is recommended NHS England at minimum be aware, of the clean team negotiations. It is advised that NHS England be engaged from early in the process but at a minimum at this stage. The Arbitrator may share his/her recommendation on the value attribution with NHS England. As the ACD consultation period is limited to 4 weeks, there may be a requirement of pause the process whilst re-negotiations and discussions with NHS England take place. The Framework aims for re-negotiations to be concluded within the standard allocated NICE timeline, but due to the complexity of these negotiations, a pause in the process may be required. The Authors suggest a time limited pause be available.	Depending on the difference between the lead manufacturer assumptions in the original submission and the Committee preferred assumptions in the ACD, and the corresponding incremental value and ICERs, extensive re-negotiations may be required. In the event of significant divergence in the estimated incremental value, a pause may be required to enable for renegotiations with the clean teams to take place. The Authors note that within current appraisals, the NICE process is at times paused whilst challenging issues and commercial arrangements are discussed between NHS England and the manufacturer. The Authors consider that a time limit on the negotiation (and pause to the NICE process) may be required to incentivise a resolution and prioritise patient access. Further work is required to set an acceptable pause period for all stakeholders however the Authors emphasise the objective to avoid undue delay. Should the Committee be minded to recommend the combination treatment to the CDF, the Authors consider it possible to agree mechanisms to address data uncertainties through this process, even though multiple manufacturers are involved.
4b: No resolution	
If there is no resolution, the allowable pause time lapses or one manufacturer withdraws from the process, the Arbitrator will make a determination that progress cannot be made and will issue a statement setting out the facts of the situation. The lead (add-on) manufacturer may still engage with NHS England to agree to commercial access agreement (CAA) for their component of the treatment only.	The Authors feel it is important a statement of facts be issued by the Arbitrator in the event of no resolution. This will ensure manufacturers are adhering to the principles outlined in the proposed Framework and act as evidence of manufacturers' best-endeavours (if observed). The Authors recognise a commercially viable CAA may not be possible for all combination treatments, and therefore have proposed the

[1] For the purposes of the Framework, this is the latest point at which NHS England may commence negotiations. However, if all parties agree it would be beneficial to negotiate earlier, the Framework does not preclude this from happening.

If there is no commercially viable CAA and the Committee deems the combination treatment to not be cost-effective, a negative FAD will be issued by NICE.	ability for either manufacturer to walk away from the Voluntary Arbitration. In this event, the lead manufacturer may still proceed with NHS England discussions for their treatment. The Authors propose the Arbitrator be responsible for enforcing the time limit.
4c. Agreement formalised in commercial access agreement	
If a negotiated settlement is reached, the Authors would expect that it would need to be formalised in a CAA between each manufacturer and NHS England. The agreement will be confidential and may be specific to the combination. The net prices from the CAA will be used to inform the costs of the combination treatment and will be used by NICE for decision making.	The concept and terminology of 'commercial access agreement' (CAA) is widely understood within industry and the NHS. The Authors propose managed access agreements also be permitted in order to ensure the process does not entail the reduction of flexibilities available under other processes which may otherwise have been engaged (notably the CDF).
Phase 5: final guidance	
Step H(i). NICE issues positive FAD	
In the event of either a positive recommendation from the first committee meeting or second committee meeting (if required), NICE will issue a positive FAD (as now).	n/a
Step H(ii). NICE issues negative FAD	
In the event that the Committee does not find the combination treatment to be cost-effective use of NHS resources, or no viable commercial access agreement is reached with NHS England, NICE will issue a negative FAD.	n/a
Step I. NICE issues final guidance	
NICE will issue final guidance reflecting its FAD once the appeal period has passed.	n/a
Phase 6. NICE re-review or post-CDF review (if applicable)	
5. Clean teams re-formed for re-review. Discussions chaired by Arbitrator	
For completeness, the option of a NICE re-review (i.e., for treatments recommended to the CDF), clean teams will be re-engaged and resume negotiations, facilitated by the Arbitrator. The re-negotiation will be in line with NICE's existing re-review processes. The starting point for negotiations will be the negotiation outcome and corresponding CAA which led to the original FAD but will consider the new data. Any change to the CAA will need to be agreed with NHS England and each manufacturer directly.	

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