Making Solutions Transactable for Combination Treatments in a Not Cost-Effective at Zero Price Scenario:

A Conceptual Implementation Framework

December 2024

C-ANPROM/GB/OG/0734 December 2024

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Acknowledgements
Development of this Whitepaper was initiated and funded by Takeda UK Ltd.

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

Advisory panel members
Andrew H. Briggs (London School of Hygiene & Tropical Medicine)
Sarah Davis (ScHARR)
Anthony Hatswell (Delta Hat Ltd)
Martin Kaiser (Consultant Haematologist, The Royal Marsden)
Francois Maignen (NICE)
Neil Rabin (Consultant Haematologist, University College London Hospitals)
Ashley Summerfield (NHSE)
Jack Turner (NHSE)
Paul Weinberger (NHSE)
Sarah Wilkes (NICE)

It should be noted that the above individuals participated in the advisory panel as subject experts rather than representatives of their respective organisations. Some of the views expressed in this Whitepaper may not represent the views of all advisory panel members.

Takeda UK Ltd
Jade Bridger
Jerome Penn
Gemma Kay
Emma Roffe

In addition, the authors would like to acknowledge Jean Mossman (Independent Consultant) and Talya Underwood (Anthos Communications Ltd) for their review of the initial drafts.

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Abbreviations and Acronyms

ABPI	Association of the British Pharmaceutical Industry
CLT	Commercial Liaison Team
CMA	Competition and Markets Authority
DSU	Decision Support Unit
EAG	External Assessment Group
HTA	Health Technology Assessment
ILAP	Innovative Licensing and Access Pathway
MHRA	Medicines and Healthcare products Regulatory Agency
NIHRIO	National Institute for Health and Care Research Innovation Observatory
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
QALY	Quality-adjusted life year
VPAG	Voluntary Scheme for Branded Medicines Pricing, Access and Growth
VPAS	Voluntary Scheme for Branded Medicines Pricing and Access

Executive Summary

BACKGROUND

A combination treatment combines two or more individual components to achieve a therapeutic outcome for a disease.[1] Combination treatments are expected to increase clinical efficacy as the components have complementary or synergistic pharmacodynamic effects. In recent years, there has been a particular focus on combination treatments for cancer.

However, since 2017, half of all cancer combination treatments involving branded components submitted for assessment to the National Institute for Health and Care Excellence (NICE) have withdrawn from the process or were assessed as not cost-effective.[2] This cost-effectiveness issue causes delays or prevents patients from accessing clinically effective treatments.

NEED FOR AN IMPLEMENTATION FRAMEWORK

Little progress had been made towards finding solutions to combination treatment cost-effectiveness issues, with many stakeholders believing it was too hard a problem to fix. Encouragingly, there has been progress in recent years, such as the 2019 Voluntary Scheme For Branded Medicines Pricing and Access (VPAS) and the publication of Takeda UK's Attribution of Value[3, 4] and Arbitration Frameworks.[5] In addition, in 2023, the Competition and Markets Authority (CMA) published a position statement on combination treatment, recognising that in some cases, a treatment combination can only be cost-effective and commercially feasible if manufacturers collaborate. As such, the CMA states that it will not prioritise investigations under the Competition Act 1998 into specific forms of engagement between medicine manufacturers that are carried out in good faith and aim to make a combination treatment available to NHS patients in the UK if certain market features are present and conditions are met. Further, the 2024 Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG) includes clear support for implementing solutions for combination treatment cost-effectiveness issues, including NHS England (NHSE)'s support for transacting a solution for combination treatments under specific circumstances. Planned consultations on the NHSE Commercial Framework in 2024 and 2025 will reflect on the CMA prioritisation statement on combination treatments and consider options for transacting such a solution. These are positive steps, but more must be done to identify and implement workable solutions so patients can access and benefit from combination treatments.

APPROACH

This Conceptual Implementation Framework (hereafter referred to as “The Framework”) was developed following an evaluation of the existing access ecosystem, including horizon scanning, early engagement, regulatory approval, Health Technology Assessment and NHSE commissioning. From this evaluation, the Framework identifies the critical points in this ecosystem, the stakeholders, and the decision-makers that need to be involved in identifying and successfully implementing the proposed solutions for combination treatment cost-effectiveness issues.

This Framework provides a starting point for NHSE, NICE, manufacturers and the ABPI to discuss and evolve existing processes and methodologies to ensure consistent patient access to combination treatments, now and in the future. It also recommends how the clinical and patient organisation communities can actively participate in this process.

RECOMMENDATIONS

The Framework outlines critical opportunities for identifying cost-effectiveness issues and implementing solutions to bring such combination treatments to patients who need them. These opportunities exist, for example, during horizon scanning, regulatory approval, technical engagement,

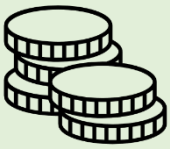
and commercial discussions. The Framework is not exhaustive, but it captures what we believe to be the main stages and stakeholders that could play a vital role in implementation.

Table 1 provides specific recommendations for stakeholders by stage in the ecosystem. Table 2 includes recommendations for broader system changes needed to create an enabling environment for implementing potential solutions for combination treatment cost-effectiveness issues.

Throughout, clear and consistent communication between manufacturers and relevant stakeholders is strongly encouraged to identify and implement solutions as early as possible and bring combination treatments to patients.

RECOMMENDATION TABLE 1: Where and how to highlight potential cost-effectiveness issues across the UK regulatory, treatment approval and commissioning pathway

Step of pathway	Recommendation
Horizon Scanning 	**Clinicians and patient organisations** • Where capacity allows, professional bodies, academic research and study groups, and patient organisations should keep abreast of pipelines, regulatory developments and upcoming NICE appraisals to highlight combinations that will be valuable to patients and which may be at risk of not being cost-effective at zero price.
	UK PharmaScan • The team responsible for maintaining and updating UK PharmaScan should implement a section encouraging manufacturers to flag potential cost-effectiveness issues. Ideally, this should be a mandatory field (adding a tick box or yes/no/maybe option if a combination treatment is unlikely to be cost-effective at zero price). • The UK PharmaScan team can also share this information with NICE to facilitate early engagement between manufacturers, NICE and NHSE and allow sufficient time for engagement and implementation of solutions. • Manufacturers should also be encouraged to flag potential cost-effectiveness issues related to combination treatments through UK PharmaScan.
	National Institute for Health and Care Research Innovation Observatory (NIHRIO) • The NIHRIO Innovation Briefings and strategic horizon scanning reports should include a section to flag combination treatments unlikely to be cost-effective at zero price.
Regulatory 	**Innovative Licensing Access Pathway (ILAP) under the Medicines and Healthcare products Regulatory Agency (MHRA)** • All Innovative Licensing and Access Pathway (ILAP) stakeholders (i.e. MHRA, NHSE, NHS Scotland, NICE, etc.) should be aware of potential cost-effectiveness issues for combination treatments and the availability of potential solutions and advise manufacturers accordingly. This could include adding a section or drop-down menu option in a relevant form. • The ILAP team should also update its processes to enable manufacturers to report and highlight cost-effectiveness issues.

Early Engagement 	NICE • The NICE Advice team should introduce systems to track potential cost-effectiveness challenges for combination treatments and provide relevant advice to manufacturers regarding the availability of solutions via its services. • NICE's Decision Support Unit should update relevant parts of its 2014 working paper on cost-effectiveness issues for combination treatments to reflect recent literature on value attribution and the emergence of other potential solutions.
Health Technology Appraisal 	NICE • NICE should review its technology appraisal steps and processes to ensure cost-effectiveness issues for combination treatments can be raised, discussed, and potentially resolved in the early stages of an appraisal. This review could include, for example, referral, scoping, and clarification questions during External Assessment Groups, Technology Evaluations, and Decision Problem Meetings. • Manufacturers and NICE/NHSE could also conduct mock appraisals to test proposed solutions to the cost-effectiveness issues in a real-world setting.
Commercialisation 	NHS England • NHSE should add specific and explicit language to its post-consultation Commercial Framework for New Medicines to support reimbursing combination treatments facing cost-effectiveness issues using appropriate and fair commercial flexibilities. Ideally, this should include, at a minimum, acceptance of non-uniform pricing. We would also recommend commercial flexibilities be considered irrespective of where the combination treatment lies within the cost-effectiveness threshold, as currently there is greater flexibility only to those sitting at the lower end of the threshold; however, we acknowledge that a change to this guiding principle of the Commercial Framework would have implications for medicines pricing. • NHSE should also include formal recognition of the CMA prioritisation statement and acknowledgement of the availability of potential solutions.

RECOMMENDATION TABLE 2: Recommendations to create an enabling environment to implement solutions that address combination treatment cost-effectiveness issues

Ongoing support from relevant stakeholders • Ongoing support from relevant stakeholders (manufacturers, ABPI, NICE, NHSE, etc.) is crucial to developing and implementing solutions to cost-effectiveness issues for combination treatments. Collaboration and commitment to resolving cost-effectiveness issues across the ecosystem will ensure that combination treatments, which otherwise may not be reimbursed, are available to patients. • Manufacturers and all other stakeholders must be willing to discuss and evaluate the solutions and demonstrate a genuine willingness to implement and adopt them. • Collectively and individually, this must be recognised as an ongoing issue and remain a priority for all stakeholders.

Clear and consistent communication between NICE/NHS England, manufacturers, and other relevant stakeholders

- To support the adoption and implementation of solutions for cost-effectiveness issues related to combination treatments, all relevant stakeholders, including NICE, NHSE, and manufacturers, should communicate clearly, consistently and regularly with all implicated stakeholders about the availability of solutions.
- Relevant staff must be trained on the latest developments and solutions for cost-effectiveness issues in combination treatments.
- A collaborative, solution-oriented mindset from all implicated stakeholders is crucial for successfully addressing the challenges and implementing solutions.

Strengthening data collection systems and ensuring data transparency

- Without robust data collection platforms, it is challenging to implement value attribution methods and commercial arrangements, as doing so is dependent on robust, high-quality, standardised data collection across NHSE.
- Better data collection platforms and systems would be valuable for all relevant stakeholders, enabling higher-quality data collection and a deeper understanding of value attribution for combination treatments. In particular, robust data collection platforms will be necessary to link data on treatment use of the specific combination in practice to allow assessment of the value of implementing potential solutions for cost-effectiveness issues.
- Throughout, relevant stakeholders should have timely access to all necessary data, although data must be anonymised and shared under confidentiality agreements to protect patient confidentiality.
- This approach aligns with the 2024 Data Protection and Digital Information Bill[23], which emphasises the need for secure, standardised, and transparent data handling practices.

Evaluation, review and feedback on solutions

- Solutions must be implemented in a learning environment where feedback is constructive. Learnings from the initial implementation of solutions by manufacturers, NICE, and NHSE should be shared as case studies to support manufacturers of combination treatments and outline good practices for the future. Specifically, NICE, External Assessment Groups and Appraisal Committees will need to be aware of the methods of value attribution, as these may be utilised when demonstrating cost-effectiveness within models contained in Health Technology Assessments.
- NHSE should consider non-uniform pricing, irrespective of where the combination treatment lies within the cost-effectiveness threshold.
- The ABPI can play a critical role in supporting learning and feedback loops by sharing anonymised data with NHSE and NICE on the progress of implemented solutions and identifying any ongoing issues. The ABPI's existing continuous feedback practices can serve as a model for this initiative.[6]

SUMMARY

Many combination treatments face significant cost-effectiveness challenges, delaying or preventing patient access. This Framework outlines critical opportunities for identifying a cost-effectiveness issue and implementing solutions to ensure patients who need combination treatments get access.

As such, the Framework should provide a basis for NHSE, NICE, manufacturers, and the ABPI to agree and implement necessary changes to enable access to effective combination treatments that otherwise may not be reimbursed. Finally, all relevant stakeholders must be willing to discuss, evaluate, and adapt the solutions and demonstrate a solid willingness to drive change within their organisations.

I: Combination Treatment Background

A combination treatment combines two or more individual components to achieve a therapeutic outcome for a disease.[1] Many combination treatments comprise a 'backbone' (a drug or drug combination already approved for use) and one or more 'add-on' treatments. The 'backbone' treatment is often the existing standard of care for a given disease, and its use in clinical practice is frequently well-established before it is combined with another treatment.

The 'add-on' treatment(s) may have been developed and introduced into clinical practice as an independent treatment or have been explicitly designed to work with a 'backbone' treatment. In the latter case, the clinical development programme and registrational trials would have been based on the combination treatment. Combination treatments are expected to increase clinical efficacy as the components have complementary or synergistic pharmacodynamic effects. These effects simultaneously target different disease receptors and pathophysiological pathways and may avoid the development of treatment resistance.

Although combination treatments are used across many types of diseases and conditions, there has been a particular focus on branded combination treatments for cancer in recent years, with many becoming part of the standard of care. For example, members of the Association of the British Pharmaceutical Industry (ABPI) with a cancer portfolio have indicated that half of their medicine pipelines are combination treatments.[1] However, the ABPI has reported that since 2017, half of cancer combination treatments involving branded treatments submitted for assessment to the National Institute for Health and Care Excellence (NICE) have withdrawn from the process entirely or were assessed as not cost-effective.[2]

II: The Cost-Effectiveness Issue for Combination Treatments

While there are many reasons why a combination treatment may be deemed not cost-effective, a particular issue is that combination treatments demonstrated to be clinically effective may be deemed not cost-effective even at a zero price. This concept was outlined by the Decision Support Unit (DSU) for NICE, which published a working paper on this phenomenon in 2014.[7] Given that nearly a decade has passed since the publication of the DSU paper, an update is long overdue to reflect the availability of recently developed solutions, address the growing complexity of combination treatments, and reflect advances in economic evaluation methods.

The Economic Evaluation of Combination Treatments: Value Assessment and the 'Not Cost-Effective at Zero Price' Paradox

New treatments and technologies are subject to rigorous clinical and economic assessment to optimise the allocation of finite healthcare resources. Cost-effectiveness analysis is a method commonly used to assess the economic value of new treatments; this method is frequently used in the UK. This approach assesses value based on how changes in healthcare costs correlate to changes in health outcomes. The quality-adjusted life year (QALY) is the standard outcome measure used in cost-effectiveness analysis. It is used as the basis for decisions because it makes it possible to compare healthcare interventions based on a common measure of value across different treatment areas and diseases.

The crux of the 'not cost-effective at zero price' issue stems from combination treatments being evaluated as a single treatment despite comprising individual treatments priced independently. The initial entrant to the market, the 'backbone' treatment, can use the entire willingness-to-pay threshold for the benefit it delivers and is unlikely to be reassessed once recommended. As the overall cost of a combination treatment includes both the backbone and add-on treatment, the add-on component has a much-reduced opportunity to be considered cost-effective. In addition, as combination treatments can potentially extend patients' survival and quality of life and are often used

on a treat-to-progression basis, even if the add-on treatment were to be given away at zero price, the cost to the healthcare system could still increase due to the backbone treatment being used for longer with the combination.

Progress to Date: Solutions for Cost-Effectiveness Challenges for Combination Treatments

Despite the DSU paper's publication in 2014, it was several more years before meaningful solutions were first discussed.

Recognition of the Issue in VPAS

In the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS), the Department of Health and Social Care tasked the ABPI with developing solutions for the not-cost-effective at zero price issue for combination treatments.[8] For the first time, this meant manufacturers, via the ABPI, had been tasked with finding a solution.

Attribution of Value Frameworks

Several interested parties were already exploring potential solutions for combination treatment cost-effectiveness issues that could meet the needs of the system's various stakeholders. Two value attribution methodology options have recently been published, including one developed by Takeda UK with input from an Advisory Group with representation from all implicated stakeholders[3]. These options propose economic methods that define a fair value division across the component parts of a combination. These methods are not discussed in this Framework, but further information can be found in Briggs et al. and OHE.[3, 4]

Anti-Trust Legislation and Arbitration Framework

In the UK, anti-trust law does not permit manufacturers to discuss the individual component prices of a treatment combination. However, the 2023 Competition and Markets Authority (CMA) "*Position Statement on Combination Therapies*" recognises that in some cases, a treatment combination can only be cost-effective and commercially feasible if manufacturers collaborate.[2] The CMA states that it will not prioritise investigations under the Competition Act 1998 (the 'CA98') into specific forms of engagement between medicine manufacturers that are carried out in good faith and aim to make a combination treatment available to NHS patients in the UK if certain market features are present and conditions are met.[9] Nevertheless, the CMA position statement also restricts component manufacturers from sharing confidential net pricing. It generally seeks to limit the information shared between suppliers.[2, 9]

This statement is the culmination of collaborative efforts led by the ABPI, which included NICE and NHSE and individual interactions with manufacturers in response to the VPAS 2019 requirement to find a solution. As with value attribution methodologies, Takeda UK has published an Arbitration Framework to enable compliant inter-company dialogue on the attribution of value and to support manufacturers in resolving disagreements without breaching competition law.[5]

2024 Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG)

The 2024 VPAG includes clear support for implementing solutions for combination treatment cost-effectiveness issues, including NHSE's support for transacting a solution for combination treatments under specific circumstances.[10] Planned consultations on the Commercial Framework in 2024 and 2025 will reflect on the CMA prioritisation statement on combination treatments and consider options for transacting a solution for combination treatments.[9]

These are positive steps, but more must be done to ensure implementation is workable for all and patients realise the potential benefit of combination treatments.
While these developments are positive steps towards enabling access to combination treatments facing cost-effectiveness issues, other elements must be considered to make any solutions implementable and transactable.

III: Implementation Approach

The Framework takes a whole-system view of implementing solutions for cost-effectiveness issues with combination treatments. It outlines opportunities, existing policy levers, and points across the combination treatment regulatory and access continuum where potential cost-effectiveness issues could be identified. It also suggests solutions that could be implemented to bring combination treatments to patients who may otherwise not be reimbursed due to cost-effectiveness issues.

It is not exhaustive, but it captures what we believe to be the main points at which potential cost-effectiveness issues could be identified when bringing a combination treatment to the market. It has been written with input from relevant stakeholders to ensure its implementation aligns with existing methods, processes, systems, policies, methodologies, etc., where appropriate or where those may need amending.

We hope this Framework will provide a starting point for NHSE, NICE, manufacturers, and the ABPI to discuss and evolve existing processes and methodologies to ensure consistent patient access to combination treatments now and in the future. We also hope it will propose a role for the clinical and patient organisation communities in actively supporting access to combination treatments.

Figure 1 provides an overview of the main points along the treatment regulatory and access pathway where potential solutions could be implemented. All relevant stakeholders must be engaged across the treatment regulatory and access continuum to implement solutions effectively.

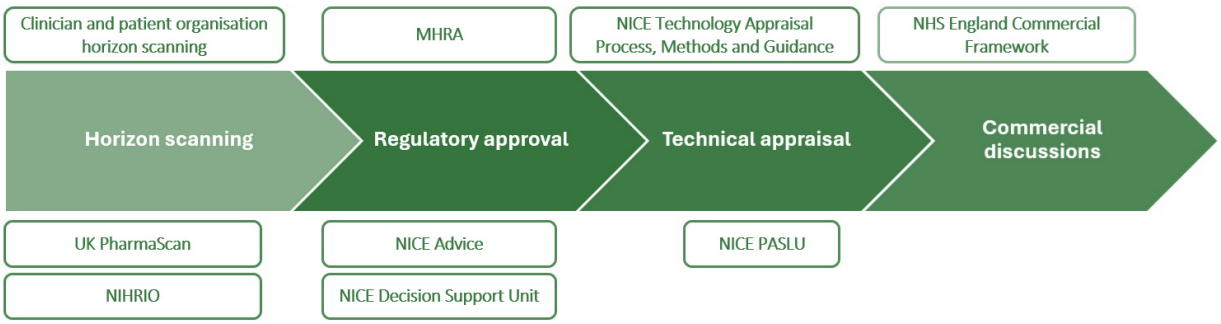


Figure 1. Opportunities to identify cost-effectiveness issues for combination treatments across the treatment regulatory and access pathway

Patient Organisation and Clinical Community Horizon Scanning

Patients and patient organisations play a vital role in driving demand for combination treatments and underlining the urgent need to find solutions for cost-effectiveness issues that prevent access to these treatments. Clinicians and their associated communities are also central in driving demand as advocates for patients to receive the most clinically effective treatments.

Clinicians, patients, and patient organisations increasingly recognise the need and the opportunity for involvement in pharmaceutical clinical development programmes. This trend is set to continue, especially with the increasing involvement of patients and patient organisations in research, regulatory, and health technology assessment (HTA) processes. In addition, many clinicians will be involved as local investigators in trials of combination treatments, and many patient organisations will have information available for patients on recruiting trials in their respective therapeutic areas.

Therefore, besides more formal horizon scanning (for example, through the National Institute for Health and Care Research Innovation Observatory [NIHRIO]), clinicians and patient organisations that are not already doing so should conduct horizon scanning in their treatment areas of interest. As part

of this, clinicians and patient organisations can highlight combination treatments that may be at risk of not being cost-effective, such as those of two or more patented components from different manufacturers.[3]

Combination treatments facing potential cost-effectiveness issues can be flagged to manufacturers at any stage when recognised by patient organisations and clinicians and through early engagement opportunities, such as NICE Scientific Advice. Clinicians and patient organisations can also highlight available solutions to resolve the issue. To enable the greater engagement of patient organisations and clinicians in horizon scanning, relevant stakeholders should seek to integrate more robust patient and clinician feedback into their processes.

Recommendation:

Where capacity allows, professional bodies, academic groups, and patient organisations should keep abreast of pipelines, regulatory developments and upcoming NICE appraisals to highlight combinations that will be valuable to patients and that may be at risk of not being cost-effective at zero price.

UK PharmaScan

UK PharmaScan is a database of information on new medicines, indications, and formulations in the pharmaceutical pipeline.[11] It is the primary source of information used by the UK's national horizon scanning organisations and NHSE to enable early engagement in planning and preparing the NHS to introduce new treatments and support faster NHSE adoption. Manufacturers regularly populate it on a confidential and secure platform. UK PharmaScan provides an early opportunity for a potential cost-effectiveness issue to be signalled by the manufacturer.

Plans for a new UK PharmaScan platform within the first three years of the 2024 VPAG aim to better support the MHRA, UK HTA assessment agencies and NHS with their horizon scanning efforts.[10] This planned platform revision provides an opportunity to implement changes that make it easier for manufacturers to report potential cost-effectiveness issues and for UK PharmaScan to share these issues with NICE and NHSE. Ideally, this would include adding one question: a tick box or yes/no/maybe option if a combination treatment is unlikely to be cost-effective. Where devolved nations create supplementary horizon scanning reports, cost-effectiveness issues should be flagged in their reporting.

Recommendations:

The team responsible for maintaining and updating UK PharmaScan should implement a section encouraging manufacturers to flag potential cost-effectiveness issues. Ideally, this should be a mandatory field (adding a tick box or yes/no/maybe option if a combination treatment is unlikely to be cost-effective). Manufacturers should also be encouraged to flag potential cost-effectiveness issues related to combination treatments through UK PharmaScan. The UK PharmaScan team can also share this information with NICE to facilitate early engagement between manufacturers, NICE and NHSE and allow sufficient time for engagement and implementation of solutions.

National Institute for Health and Care Research Innovation Observatory (NIHRIO)

The NIHRIO is the National Horizon Scanning and Intelligence Research Centre and home of health innovation future scanning.[12] Its key focus is to identify promising 'innovative medicines' that meet

the needs of the NHS. The NIHRIO provides routine outputs to NICE and the Accelerated Access Collaborative.

The NIHRIO supports the processes designed to provide recommendations (in the form of NICE guidance) on using new and existing treatments in the NHS in England. Their role is to identify, filter, monitor and produce technology briefings for all innovative treatments and technologies that meet the NICE criteria and are within five years of an estimated UK licence date. The NIHRIO Innovation Briefings represent an opportunity to flag potential cost-effectiveness issues for a combination treatment early in the system.

Recommendation:

The NIHRIO Innovation Briefings and strategic horizon scanning reports should include a section to flag combination treatments unlikely to be cost-effective.

The Innovative Licensing and Access Pathway (ILAP) under the Medicines and Healthcare products Regulatory Agency (MHRA)

Before a combination treatment can be prescribed in the UK, it must receive marketing authorisation from the MHRA. The MHRA is, therefore, one of the earliest points in the UK ecosystem where potential cost-effectiveness issues for a combination treatment could be raised. Despite the MHRA's remit being outside of cost-effectiveness, the Innovative Licensing and Access Pathway (ILAP) represents a credible opportunity for manufacturers and relevant stakeholders to raise potential cost-effectiveness issues and discuss ways in which to potentially address them.[13, 14]

For eligible treatments, the ILAP provides a significant opportunity to flag and discuss the issue, not least because it requires the MHRA to cooperate with NICE to provide a single integrated platform for sustained collaborative working. It aims to reduce the time to market and ensure that patients have timely access to new, potentially transformative treatments.

Recommendation:

All ILAP stakeholders (i.e. MHRA, NHSE, NHS Scotland, NICE, etc.) should be aware of potential cost-effectiveness issues for combination treatments and the availability of potential solutions and advise manufacturers accordingly. This could include adding a section or drop-down menu option in a relevant form. The ILAP team should also update its processes to enable manufacturers to report and highlight cost-effectiveness issues easily.

NICE

There are several opportunities within the NICE early engagement and technology appraisal processes where a potential issue of cost-effectiveness for a combination treatment could be raised and discussed. The most obvious of these are listed in this section.

NICE Decision Support Unit

In 2014, NICE published a working paper that outlined the circumstances in which health technologies that are demonstrated to be effective may nevertheless be deemed not cost-effective even at a zero price.[7] As this paper is ten years old, the DSU should consider updating it to reflect recent literature on value attribution and the emergence of potential implementable and transactable solutions.

NICE Advice Service

The recently updated and repackaged NICE Advice Service, which now incorporates the Office of Market Access provides multiple opportunities to raise, discuss and consider solutions, including Scientific Advice, NICE surgeries, therapeutic landscape reviews and system engagement meetings.[15] NICE Advice also offers manufacturers several educational opportunities in multiple formats. It is reasonable to assume and expect that the NICE Advice team could leverage all these opportunities to provide relevant advice to manufacturers on solutions for potential cost-effectiveness issues for combination treatments.

Recommendation:

The NICE Advice team should introduce systems to track potential cost-effectiveness issues for combination treatments and provide relevant advice to manufacturers regarding the availability of solutions via its services. NICE's Decision Support Unit should update relevant parts of its 2014 working paper on cost-effectiveness issues for combination treatments to reflect recent literature on value attribution and the emergence of potential solutions.

Technology Appraisal Processes, Methods and Guidance

Over recent years, the NICE appraisal process has become more iterative and collaborative, meaning several points in the process are available for solutions to be proposed and discussed.[16] These include the prioritisation stage, scoping, decision problem, and a technical engagement step if one is required. As such, manufacturers should be encouraged to engage with relevant stakeholders as early as possible around potential cost-effectiveness issues for combination treatments. We also recommend NICE technical teams and committees be trained on available solutions and how to implement them.

Commercial Liaison Team

The Commercial Liaison Team (CLT) works with manufacturers considering a patient access scheme for their treatment.[17] Patient access schemes are price discounts proposed by pharmaceutical manufacturers that aim to improve the cost-effectiveness of treatments and enable patient access. For many manufacturers, interacting with the CLT may be one of the first times when cost-effectiveness issues are raised. Therefore, the CLT could be vital in highlighting potential cost-effectiveness issues for combination treatments to manufacturers and NICE colleagues.

Mock Appraisals to Evaluate Potential Value Attribution Solutions

Manufacturers and NICE/NHSE could conduct a mock single technology appraisal to test the use of available solutions in a real-world setting. This mock appraisal could be done using a past appraisal of a combination treatment that is not cost-effective at zero price, where all components of the proposed combination treatment solutions are utilised. Such mock appraisals would demonstrate how NICE and NHSE methods and processes stand up to using the value attribution framework, whether changes should be made, and what learnings should be implemented. They would also pressure test the processes and identify any additional infrastructure considerations.

Recommendation:

NICE should review its technology appraisal steps and processes to ensure cost-effectiveness issues for combination treatments can be raised, discussed, and potentially resolved in the early stages of an appraisal. This review could include, for example, referral, scoping, and clarification questions during External Assessment Groups, Technology Evaluations, and Decision Problem Meetings. Manufacturers and NICE/NHSE could also conduct mock appraisals to test proposed solutions to the cost-effectiveness issues in a real-world setting.

NHS England Commercial Framework

The NHSE Commercial Framework for New Medicines sets out the purpose and principles on which NHS commercial medicines activities are based. The Commercial Framework provides several opportunities to highlight potential cost-effectiveness issues with combination treatments.[18] It includes clarification of commercial flexibilities that may be available to manufacturers where deemed appropriate by NHSE. These flexibilities are reserved for manufacturers aspiring to deliver greater health gains relative to costs.

Following the publication of the 2024 VPAG in January 2024, NHSE planned two consultations on updates to the Commercial Framework for New Medicines. The first, in July 2024, addressed proposed criteria for when NHSE will consider indication-specific pricing arrangements; the second is expected in summer 2025.[10] This consultation will align the Commercial Framework with updated regulatory and access pathways and ensure it is more explicit about enhanced commercial flexibilities, including for combination treatments facing cost-effectiveness issues and when they can be offered.

NHSE should add specific and explicit language to its post-consultation Commercial Framework for New Medicines to support reimbursing combination treatments facing cost-effectiveness issues using appropriate and fair commercial flexibilities. Ideally, this should include, at a minimum, acceptance of non-uniform pricing. We would also recommend commercial flexibilities be considered irrespective of where the combination treatment lies within the cost-effectiveness threshold, as currently there is greater flexibility only to those sitting at the lower end of the threshold. However, we acknowledge that a change to this guiding principle of the Commercial Framework would have implications for medicines pricing.

The language should also include formal recognition of the CMA prioritisation statement and acknowledgement of the availability of potential solutions.[3,5] For combination treatments that are unlikely to be cost-effective, it is essential that they still receive commercial flexibilities, as these treatments are effectively pushed to the lower end of the willingness-to-pay threshold, a position typically required for treatments to qualify for such flexibilities.

Engagement with all relevant stakeholders regarding the Commercial Framework for New Medicines is essential to ensure the inclusion of fair and appropriate flexibility for cost-effectiveness issues for combination treatments. As per the 2024 VPAG, NHSE will support transacting a solution for combination therapies under specific circumstances, in line with the CMA prioritisation statement.[10] Engaging with clinicians and patient organisations is essential to consider their voices appropriately in these consultations.

In addition, as part of the current NHSE Commercial Framework, manufacturers can request pipeline and commercial surgeries, which are excellent opportunities to flag and address potential downstream cost-effectiveness issues for combination treatments. Once a potential issue is identified in the NIHIRO briefing note or NICE scoping, a commercial surgery should immediately be offered. For these and many other reasons, the NHSE Commercial Framework will be a vital platform to support the implementation of solutions for combination treatment cost-effectiveness issues.

Recommendation:

NHSE should add specific and explicit language to its post-consultation Commercial Framework for New Medicines to support reimbursing combination treatments facing cost-effectiveness issues using appropriate and fair commercial flexibilities. Ideally, this should include, at a minimum, acceptance of non-uniform pricing. We would also recommend commercial flexibilities be considered irrespective of where the combination treatment lies within the cost-effectiveness threshold, as currently there is greater flexibility only to those sitting at the lower end of the threshold. However, we acknowledge that a change to this guiding principle of the Commercial Framework would have implications for medicines pricing. NHSE should also include formal recognition of the CMA prioritisation statement and acknowledgement of the availability of potential solutions.

IV: Creating an Enabling Environment to Implement Solutions for Combination Treatment Cost-Effectiveness Issues

This Framework identifies critical points in the system where cost-effectiveness issues with combination treatments should be raised and where potential solutions should be implemented. Resolving cost-effectiveness issues with combination treatments will require engagement and commitment from all relevant stakeholders across the combination treatment development pathway. There must be change across the system and definitive, tangible steps taken to support the implementation of solutions that can provide patients access to combination treatments that face cost-effectiveness issues. Here, we share recommendations for broader system changes needed to create an enabling environment for implementing potential solutions for combination treatment cost-effectiveness issues.

Ongoing Support from Relevant Stakeholders

Ongoing support from all relevant stakeholders (manufacturers, ABPI, NICE, NHSE, etc.) is crucial to developing and implementing potential solutions to cost-effectiveness issues for combination treatments. Collaboration and commitment to resolving cost-effectiveness issues across the ecosystem will ensure that such combination treatments, which may not otherwise be reimbursed, are available to patients. As a first step, we hope that relevant stakeholders will consider the recommendations here and the actions that could be taken to implement solutions where they operate in the treatment development pathway.

Clear and Consistent Communication from NICE/NHSE to Relevant Stakeholders

To support the adoption and implementation of solutions, NICE, NHSE, manufacturers, and other system stakeholders should communicate clearly, consistently, and regularly about the availability of solutions for cost-effectiveness issues in combination treatments. Relevant stakeholders must also know the latest updates and solutions for this issue.

Strengthening Data Collection Systems

Without robust data collection platforms, implementing value attribution methods is challenging, as doing so is dependent on robust, high-quality, standardised data collection across NHSE. For manufacturers and the system to have faith in implementing potential solutions, there is a need to strengthen data collection systems so that these data can be collected, collated, and shared with relevant stakeholders to ensure any solutions are transactable. Notably, simulations conducted by companies as part of the CMA process have identified robust data collection as a major requirement for executing any agreements. This underscores the critical need for enhanced data systems to support effective collaboration and decision-making.

Despite the potential benefit of collecting data on treatment use, longstanding barriers have prevented the NHS from realising this potential. These barriers have included lacking linked data with

detailed clinical information, data quality and fragmentation issues, and a need for a larger analytical workforce to support data collection and analysis.[19-21] Political events, major public health events, and NHS reorganisations have compounded challenges in scaling up quickly and effectively, leaving risks to safety, outcomes, health inequalities, and public trust.[19-21]

Better data collection platforms and systems would be valuable for all stakeholders to enable a deeper understanding of value attribution for combination treatments. Effective data collection platforms will be necessary to link data on treatment use in practice with revenue and to allow assessment of the value of implementing potential solutions. The Department of Health and Social Care's new digital health and social care plan provides a significant opportunity to strengthen data collection across the NHS.[22] Additionally, conducting a mock appraisal could allow NICE to test different data collection options and identify any additional infrastructure considerations.

Improving data collection and transparency can help us identify when patients are prescribed a combination treatment and when a specific price is applicable. This information will also help track the longevity of treatments for commercial agreements between two manufacturers, as described in the CMA position paper. Relevant stakeholders should have timely access to all necessary data, although data must be anonymised and shared under confidentiality agreements to protect patient confidentiality. This approach aligns closely with the 2024 Data Protection and Digital Information Bill[23], which emphasises the need for secure, standardised, and transparent data handling practices.

Evaluation, Review, and Feedback on Solutions

All relevant stakeholders must be willing to discuss and evaluate the potential solutions to address the cost-effectiveness issues for combination treatments and demonstrate a solid willingness to implement and adopt them. Specifically, NICE, External Assessment Groups and Appraisal Committees will need to be aware of the methods of value attribution, as these may be utilised when demonstrating cost-effectiveness within models contained in Health Technology Assessments.[3, 4] Few, if any, existing methods are perfect. However, they get better with time and use. This will also be the case for the value attribution methodology, which must be applied, reviewed and improved.

Likewise, with NHSE, we hope there will be a willingness to consider non-uniform pricing, irrespective of where the combination treatment lies within the cost-effectiveness threshold. Currently, greater flexibility is available only to those sitting at the lower end of the threshold, as well as formal recognition of the CMA prioritisation statement and acknowledgement of the availability of potential solutions.

These solutions must be implemented in a learning environment where feedback is constructive. Learnings from the initial implementation of solutions from manufacturers and NICE/NHSE should be shared as case studies to support manufacturers of combination treatments and outline good practices for the future. The ABPI can also play a critical role in supporting learning and feedback loops by sharing anonymised data with NHSE and NICE on the progress of implemented solutions and identifying any ongoing issues. The ABPI's existing continuous feedback practices can serve as a model for this initiative.[6]

V: Conclusion

Combination treatments are becoming increasingly common, and many deliver significantly improved patient clinical outcomes, particularly in cancer. However, persistent issues remain around assessing and appraising some combination treatments as part of a cost-effectiveness HTA, which can lead to delays and prevent patient access. Notably, clinically effective combination treatments may be deemed not cost-effective even at a zero price. This issue must be addressed to ensure patients can access these treatments, which may otherwise not be reimbursed for use in NHSE.

This Framework has outlined critical opportunities to identify combination treatments that may be facing cost-effectiveness issues, as well as opportunities to implement solutions to ensure patients who need such treatments get access. As such, it should provide a basis for NHSE, NICE, manufacturers, and the ABPI to agree and implement necessary changes to enable access to effective combination treatments that otherwise may not be reimbursed for use in NHSE.

Key messages:

- Patients ultimately face the consequences of cost-effectiveness issues with combination treatments, as they are left unable to access the benefits of clinically effective treatments.
- All relevant stakeholders must be willing to discuss, evaluate, and adapt the solutions for combination treatment cost-effectiveness issues and demonstrate a strong willingness to drive change within their organisations towards acceptance and adoption.
- Recognising that adaptations and updates may be required to assist with the optimal implementation of solutions, we welcome feedback and the sharing of learnings from all stakeholders, including clinicians and patient organisations.

The Framework presented here is a basis for NHSE, NICE, manufacturers and the ABPI to take further steps in agreeing and implementing the necessary changes to enable patient access to effective combination treatments.

Reference list

1. Association of the British Pharmaceutical Industry. Patient access to combination therapies, https://www.abpi.org.uk/value-and-access/patient-access-to-combination-therapies/ (accessed December 2024).

2. Competition and Markets Authority. CMA removes barrier to availability of vital treatments on the NHS, https://www.gov.uk/government/news/cma-removes-barrier-to-availability-of-vitaltreatments-on-thenhs#:~:text=The%20Association%20of%20the%20British,the%20process%20entirely%20or%20were (2023, accessed December 2024).

3. Briggs AH, Doyle A, Schneider J, et al. An Attribution of Value Framework for Combination Therapies, https://assets-dam.takeda.com/raw/upload/v1675187100/legacy-dotcom/siteassets/engb/home/what-we-do/combination-treatments/a-value-attribution-framework-for-combinationtherapies-takeda-whitepaper.pdf (2021, accessed December 2024).

4. Towse A, Lothgren M, Steuten L, et al. Why we need a new Outcomes-based Value Attribution Framework for Combination Regimens in Oncology, OHE Consulting Report, https://www.ohe.org/wpcontent/uploads/2021/02/Outcomes-based-VAF-final-v2-clean-2.pdf (2021, accessed December 2024).

5. Podkonjak T, Taylor H, Taylor A, et al. Voluntary Arbitration Framework for Combination Therapies, https://assets-dam.takeda.com/raw/upload/v1662722975/legacy-dotcom/siteassets/engb/home/what-we-do/combinationtreatments/VoluntaryArbitrationFrameworkforCombinationTherapies_TakedaWhitepaper_Septembe r2021.pdf (2021, accessed December 2024).

6. Association of the British Pharmaceutical Industry. Reviewing the impact of the updated NICE Health Technology Evaluation Manual (CONNIE), https://www.abpi.org.uk/publications/reviewing-theimpact-of-the-updated-nice-health-technology-evaluation-manual-connie/ (2023, accessed December 2024).

7. University of Sheffield NICE Decision Support Unit. Not cost-effective at £0, https://www.sheffield.ac.uk/nice-dsu/methods-development/not-cost-effective-ps0 (accessed December 2024).

8. Department of Health and Social Care. Policy paper: Voluntary scheme for branded medicines pricing and access, https://www.gov.uk/government/publications/voluntary-scheme-for-brandedmedicines-pricing-and-access (2022, accessed December 2024).

9. Competition and Markets Authority. Combination therapies: prioritisation statement, https://www.gov.uk/government/publications/combination-therapies-prioritisation-statement (2023, accessed December 2024).

10. Department of Health and Social Care. Policy paper: 2024 voluntary scheme for branded medicines pricing, access and growth, https://www.gov.uk/government/publications/2024-voluntaryscheme-for-branded-medicines-pricing-access-and-growth (2023, accessed December 2024).

11. UK PharmaScan. https://www.ukpharmascan.org.uk/ (accessed December 2024).

12. National Institute for Health and Care Research Innovation Observatory. About, https://www.io.nihr.ac.uk/about/ (accessed December 2024).

13. Medicines and Healthcare products Regulatory Agency. Innovative Licensing and Access Pathway, https://www.gov.uk/guidance/innovative-licensing-and-access-pathway (2024, accessed December 2024).

14. Medicines and Healthcare products Regulatory Agency. Apply for the early access to medicines scheme (EAMS), https://www.gov.uk/guidance/apply-for-the-early-access-to-medicinesscheme-eams (2023, accessed December 2024).

15. The National Institute for Health and Care Excellence. NICE Advice service, https://www.nice.org.uk/about/what-we-do/life-sciences/nice-advice-service (accessed December 2024).

16. National Institute for Health and Care Excellence. Technology appraisal guidance, https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technologyappraisal-guidance (accessed December 2024).

17. National Institute for Health and Care Excellence. Patient Access Schemes Liaison Unit, https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit (accessed December 2024).

18. NHS England. NHS commercial framework for new medicines. 2022 update, https://www.england.nhs.uk/publication/nhs-commercial-framework-for-new-medicines/ (2022, accessed December 2024).

19. Ghafur S, O'Brien N, Howitt P, et al. NHS data: Maximising its impact for all., https://spiral.imperial.ac.uk/bitstream/10044/1/103404/8/NHS%20Data%20%20Maximising%20Impact%20for%20All.pdf (2023, accessed December 2024).

20. Department of Health and Social Care. Better, broader, safer: using health data for research and analysis, https://www.gov.uk/government/publications/better-broader-safer-using-health-datafor-research-and-analysis (2022, accessed December 2024).

21. Department of Health and Social Care. Data saves lives: reshaping health and social care with data, https://www.gov.uk/government/publications/data-saves-lives-reshaping-health-and-socialcare-with-data/data-saves-lives-reshaping-health-and-social-care-with-data (2022, accessed December 2024).

22. Department of Health and Social Care. Policy paper: A plan for digital health and social care, https://www.gov.uk/government/publications/a-plan-for-digital-health-and-social-care (2022, accessed December 2024).

23. UK Parliament: Data Protection and Digital Information Bill. https://bills.parliament.uk/bills/3430 (2024, accessed December 2024)