Solving the challenge of combination treatments: Economic Roundtable on access to combination treatments in the UK

Chaired by Eric Low

Thursday 25 November 2021, 14:00 – 16:00, held virtually (MS Teams)

Meeting Report

Introduction

This Report summarises an economic roundtable on solving the challenge of access to combination treatments in the UK. The event was hosted by Takeda UK Ltd. and took place on Thursday, 25 November 2021.

All the perspectives captured within this Report have been anonymised, and attendance at the Roundtable does not indicate endorsement of Takeda's proposed solution. The Report should not be considered a consensus document; it is a balanced reflection of the discussion at the Roundtable. The National Institute for Health and Care Excellence (NICE) was an observer in the discussions; participation does not indicate endorsement by NICE of this Report.

Those in attendance at the Roundtable have been given the opportunity to comment on this Report.

Attendee list

The following individuals were present during the meeting:

Speakers

- Eric Low (Chair), Independent Consultant and Chair of Takeda UK's Combination Treatments Advisory Group.
- Professor Andrew Briggs, *Director, Avalon Health Economics;* Professor of Health Economics, London School of Hygiene & Tropical Medicine.
- Sarah Davis, *Deputy Director, NICE Decision Support Unit;* Senior Lecturer in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield.

Participants

- Fleur Chandler, Head of Market Access UK and Ireland, Sanofi.
- Professor Neil Hawkins, Professor of Health Economics & Health Technology Assessment, University of Glasgow.
- Dr Nick Latimer, Reader in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield.
- Dawn Lee, Chief Scientific Officer, BresMed.
- Professor Carole Longson, Senior Advisor and Consultant in Life Science Policy, HTA and Market Access; NICE Life Science Adviser.
- Jean Mossman, Visiting Senior Research Associate, London School of Economics.
- Adele Schulz, Pricing Operations Manager, Sanofi.
- Professor Lotte Steuten, Head of Consulting and Vice President, Office of Health Economics.

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- Gavin Stewart, Market Access Team Lead, AstraZeneca.
- Professor Adrian Towse, Director Emeritus, Office of Health Economics.
- David Trueman, Director, Source Health Economics.
- Darshan Zala, Health Economist, Amgen.

Takeda
- Sophie Caseby, Market Access Manager – Oncology, Takeda UK Ltd.
- James Davies, Market Access Medical Writer, Takeda UK Ltd.
- Tanja Podkonjak, Director of Access and Reimbursement Policy, EUCAN (Oncology), Takeda Pharmaceuticals International AG.
- Helen Taylor, Programme Realisation Manager, Takeda UK Ltd.

Purpose

The purpose of the Roundtable was to consider the combination treatment access challenge and to solicit feedback on a proposed solution developed by Takeda UK, supported by Professor Andrew Briggs, Alexis Doyle, John Schneider (Avalon Health Economics), Eric Low (Eric Low Consulting), Sarah Davis (University of Sheffield), Martin Kaiser (Royal Marsden NHS Foundation Trust), Anthony Hatswell (Delta Hat) and Neil Rabin (University College Hospital, London). Given the attendees' expertise, particular attention was paid to Takeda's proposed Value Attribution Methodology.

Takeda's approach to developing the solution and the components making up the solution is detailed in two Whitepapers: *An Attribution of Value Framework for Combination* Whitepaper[1] and the *Voluntary Arbitration Framework for Combination Treatments* Whitepaper.[2]

The Roundtable covered the following:

- Background to the access challenge for combination treatments
- Takeda's proposed solution
- Gathering feedback on the Value Attribution Methodology to refine the proposed solution
- Feedback on Takeda's engagement strategy and inclusion of the health economics community
- Summary of actions and next steps.

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Summary of the key discussion points

The following are the key highlights from the Roundtable; further details of the discussions can be found later in the Report.

- Until the challenges associated with access to combination treatments are addressed, patients may be unable to benefit from access to treatments that have the potential to improve the length and quality of their lives *(see Section 1).*
- The cost-effectiveness challenges associated with the appraisal of combination treatments were first reported in 2014. Solutions are overdue to enable access whilst achieving value for money for healthcare systems *(see Section 2).*
- Takeda's proposed solution is made up of two component "Frameworks" that are intended to be used together; the Value Attribution Framework (to attribute value to each treatment) and the Voluntary Arbitration Framework (to ensure compliance with competition law) *(see Sections 3 and 4, respectively).*
- There was broad support and positive feedback from attendees for the proposed Value Attribution and Voluntary Arbitration Methodologies – the Value Attribution Framework was perceived as practical and relatively simple to implement, and the participants agreed that the underlying methodology was generally sound. This was supported by participants who have applied the Framework retrospectively.
- Participants identified some potential challenges for implementation, including the lack of data on monotherapy treatments, uncertainties in analysis assumptions and base-case incremental cost-effectiveness ratios (ICERs), and confidentiality of information in health technology assessment (HTA) submissions, notably existing confidential discounts *(see Section 5).*
- Participants agreed that negotiations could become resource intensive. It therefore may be necessary for HTA bodies and or the payer to become involved in the process due to issues of confidentiality and uncertainty of base-case ICERs. However, there was concern over the possible burden placed on HTA bodies and the NHS *(see Section 5).*
- It was acknowledged that the Value Attribution Framework could provide a starting point for negotiations between companies with vested interests and strategies. All stakeholders, including HTA bodies and payers, would need to accept responsibility and contribute to a solution *(see Section 5).*

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Detailed Report of the Roundtable

1. The challenges posed by combination treatments: introduction by Eric Low

Eric Low (Chair of Takeda UK's Combination Treatments Project Advisory Group) introduced the aims of the Roundtable and provided attendees with an overview of the background to Takeda's proposed solution.

During his introduction, Mr Low outlined that:

- With the increased understanding of complex diseases and the pathways involved, combination treatments are becoming more common, particularly in oncology.
- Despite the potential benefits of combination treatments to patients, they often face cost-effectiveness barriers and, in some cases, maybe found to be not cost-effective even if the new add-on treatments were to be given away at zero or near zero price.
- There is broad agreement amongst stakeholders that a solution is required to the cost-effectiveness challenges facing combination treatments so that patients are not denied access to treatments that have the potential to improve the length and quality of their lives.
- The proposed methodologies were developed with the objectives of being practical to implement and acceptable to all stakeholders, so suggestions for further stakeholder engagement and dissemination were welcome.
- The methodologies proposed by Takeda are not finalised, so feedback would be used to inform further refinement.
- The purpose of the Roundtable was to solicit constructive critique of the methodologies proposed by Takeda and to continue to build consensus and shared understanding of the methodologies needed to address the cost-effectiveness challenge.

Further detail on the background, rationale and development of Takeda's proposed solution can be found in the *An Attribution of Value Framework for Combination* Whitepaper[1] and the *Voluntary Arbitration of a Value Attribution Framework for Combination Therapies* Whitepaper.[2]

2. Not Cost-Effective at Zero Price: An Issue When Evaluating Combination Therapies– a presentation by Sarah Davis

Sarah Davis (Deputy Director, NICE Decision Support Unit [DSU]; Senior Lecturer in Health Economics, University of Sheffield, and member of Takeda UK's Combination Treatments Project Advisory Group) provided attendees with an overview of the issues associated with evaluating the cost-effectiveness of combination treatments.

During her presentation, Ms. Davis noted that:

- Health technologies are deemed cost-effective if the incremental cost is less than the value of the quality-adjusted life years (QALYs) gained; therefore, if the incremental cost of a treatment is greater than the incremental value of the QALYs, cost-effectiveness can usually be achieved by a reduction in price.
- In 2014, the NICE DSU published a report detailing four scenarios in which it is not possible for a new treatment to be cost-effective, regardless of the price.[3] One scenario explored is where a combination treatment increases survival, leading to longer periods

of treatment and, therefore, additional acquisition and administration costs. In some situations, the costs of the existing (backbone) treatment relative to the QALY gains may be too high for the add-on treatment to be cost-effective, even if the add-on treatment were to be provided at zero cost.

- An example identified in the NICE DSU report was the addition of pertuzumab to trastuzumab and docetaxel for the treatment of HER-2 positive metastatic or locally unresectable breast cancer.[4] Both pertuzumab and trastuzumab are continued during a period of progression-free survival, leading to an annual cost for the progression-free state of greater than £20,000 per QALY, even when assuming zero cost for pertuzumab.[3]
- Common themes across all four scenarios discussed in the NICE DSU report included:
    - High costs incurred during periods of additional survival, such as best supportive care costs or the addition of new drugs (add-on treatment) to existing high-cost treatment regimens (backbone treatments).[3]
    - Additional survival periods gained at the end of life, when the quality of life is low, limiting the amount that can be spent on life-extending treatments while remaining cost-effective.[3]
- Solutions are needed to ensure that patients can access clinically effective combination treatments whilst achieving overall value for money for the healthcare systems.

3. Towards a Value Attribution Solution for Combination Therapies: a presentation by Professor Andrew Briggs

Following Ms. Davis' overview of the challenge of evaluating combination treatments, Prof. Andrew Briggs (Director, Avalon Health Economics; Professor of Health Economics, London School of Hygiene & Tropical Medicine, and member of Takeda UK's Combination Treatments Project Advisory Group) provided attendees with an outline of the proposed Value Attribution Framework, which aims to define a fair division of value across the treatments in a combination by assigning a relative value to each treatment based on the incremental health benefit.

During his presentation, Prof. Briggs noted that:

- Following the Advisory Group feedback on the requirements for a solution, the proposed methodology is based on current conventional cost-effectiveness analysis techniques. Furthermore, it is independent of existing pricing structures and agnostic to the willingness-to-pay threshold.
- In developing the Value Attribution Framework, two contextual factors were considered:
    - perfect or imperfect information about the effect of each component treatment as monotherapies, and,
    - the balance or imbalance of market power between the manufacturers of the component treatments.
- Based on these factors, the Whitepaper outlines four scenarios: 1) perfect information and balance of market power, 2) imperfect information and imbalance of market power, 3) imperfect information and balance of market power, and 4) imperfect information and imbalance of market power.
- In the perfect information scenarios, the effects of a combination may be sub-additive (the health benefits of the combination are less than the sum of the component monotherapy outcomes) or synergistic (the combination treatment is more effective than

the sum of the component outcomes). It is expected that the sub-additive scenario will be representative of most cases.

- In many cases, however, the independent values of the component treatments will not be known (i.e., clinical data on the value of each combination component as a monotherapy in the indication is not available; the add-on was only investigated as a part of the combination), leading to an imperfect scenario and subsequent challenges in determining the relative benefit of each component.
- The Whitepaper considers bargaining power in pricing negotiations positively correlated to market share. The manufacturer of a backbone treatment with an established market share is assumed to hold more bargaining power than that of a manufacturer of a new entrant add-on treatment.
    - If there is an imbalance in market share, the manufacturer with greater market share has less incentive to reduce its drug price. As a result, the manufacturer with a lower market share may incur a disproportionate share of the cost reduction needed to make the combination cost-effective.
    - A common scenario of imbalance of market power is where the backbone treatment is already available and is the standard of care in the setting, and the add-on treatment has not yet been launched; the backbone manufacturer has more market power than the add-on manufacturer.
- The Voluntary Arbitration Framework proposes a procedure for negotiations between manufacturers. The Value Attribution Framework is intended as a fair starting point for negotiations, particularly when the manufacturer of a backbone treatment is asked to provide a discount to accommodate an add-on treatment.

Professor Briggs continued by presenting two example scenarios, covering perfect and imperfect monotherapy information. Case studies of these scenarios can be found in the Value Attribution Framework Whitepaper.

4. The Voluntary Arbitration Framework: a presentation by Tanja Podkonjak

Following Prof. Briggs' overview of the Value Attribution Framework, Tanja Podkonjak (Director of Access and Reimbursement Policy, EUCAN (Oncology), Takeda Pharmaceuticals International AG) provided attendees with an overview of the key requirements identified by the Advisory Group required for a solution to be implementable and presented an outline of the proposed Voluntary Arbitration Framework.

During her presentation, Ms Podkonjak noted that:

- Even with a Value Attribution Methodology, there is currently no compliant method by which two companies can engage in dialogue to negotiate on the attribution of value.
- Therefore, a second *Voluntary Arbitration for Combination Treatments* Whitepaper was developed to propose a standard operating procedure to support compliant dialogue and agreement between pharmaceutical companies on the value attributed to each treatment within a combination.
- The proposed solution was developed based on a thorough assessment of the requirements for an implementable solution identified by the Advisory Group. These requirements were:
    - Deliver improved patient access to combination treatments

    - Be compatible with existing HTA methods and processes
    - Adhere to existing cost-effectiveness thresholds
    - Address competition law issues
    - Encourage manufacturers to work together.
- The proposed Framework is intended to run alongside the NICE Single Technology Appraisal process, beginning as early as the horizon scanning stage and with as much negotiation as possible occurring before submission to NICE. However, the Framework was developed using NICE as a reference market; the Framework can be adapted and applied to other HTA systems.
- The Framework proposes the appointment of an independent third-party Arbitrator to facilitate the negotiation and issue a non-binding recommendation on value attribution in case of an impasse.
- In addition to the independent Arbitrator, it is proposed that external 'clean teams' discuss and agree on the value attributed to each component treatment to separate the information shared during negotiation from either manufacturer's wider business.
- The Framework proposes a mandatory long-term commitment on companies to participate, with the voluntary implementation of the outcome to allow companies the autonomy to walk away if required. This commitment would be based on the expectation that, over time, companies would be the manufacturer of both the backbone and add-on treatments and would stand to benefit from an established Framework being available.

5. Refining the proposals and gathering feedback on the Value Attribution Methodology: group discussion

Following the presentations on the cost-effectiveness challenges associated with combination treatments and Takeda's proposed solution, the Chair opened the discussion. Specifically, he asked participants to provide their opinion on the rigour and validity of the Value Attribution Methodology and to identify any gaps or uncertainties in the current proposal that need to be considered.

Participants were very complimentary of Takeda's efforts to find a solution to the cost-effectiveness challenges associated with the appraisal of combination treatments. It was noted that all stakeholders must recognise that the DSU report on this topic was published in 2014. Although there have been recent positive developments since then with groups exploring options, the issue remains unresolved and therefore, an urgent solution is needed. In addition to the feedback received on the Value Attribution Methodology, participants posed a series of broader questions about the proposed solution and its implementation, as well as suggestions on how to develop it further. The feedback can be broadly split into four key themes, as follows:

1. <u>Value Attribution Methodology</u>

- Feedback indicated that the Whitepaper communicated with clarity on both the issue and the proposed solution.
- Participants agreed that the Value Attribution Methodology was generally sound and seemed practical and implementable; attendees who trialled the Value Attribution Methodology in past cost-effectiveness projects reported it was simple to implement without additional time or resources required.

- It was noted that the wider context must not be ignored – the Framework aims to address a complex problem, and as such, it would likely only provide a starting point to complex negotiations. Despite this, it was acknowledged that the existence of a framework is always helpful, even if it only provides an initial basis for further discussion.
- The scenario of imperfect information and an imbalance of market power was highlighted as both the most likely and most problematic; negotiation will be required to agree on a fair split of value between component treatments but is likely to be the most difficult to achieve.
- Participants highlighted the current challenge of determining the incremental value of an add-on treatment when its value as a monotherapy is unknown due to the lack of monotherapy clinical data. Without a method of assigning additive value, this situation may lead to add-on treatments being trialled as monotherapies to determine the agent's value, with a low likelihood of the treatment being used as a monotherapy. This would potentially lead to ethical issues associated with recruiting patients to trials of monotherapy treatments with limited potential benefits and a waste of resources. To prevent this, it is integral to develop and agree on a method of attributing value to an add-on treatment investigated in combination only.
- In synergistic scenarios, there may be potential issues of fairness when relying on monotherapy data for value attribution, as the monotherapy value of each component may not be a true representation of the value contribution per component when used in combination.
- In terms of practical application, it was noted that, due to numerous uncertainties, it is rare for a NICE appraisal committee to have a preferred set of base-case assumptions; instead, decision making is likely to be based on a range of plausible costs, QALYs and incremental cost-effectiveness ratio (ICER) estimates. Due to this uncertainty, particularly when data are redacted as confidential, it may be challenging to find a starting point for the QALY gain for each treatment. Similarly, it may be necessary to review any modifiers applied during the backbone treatment's original appraisal and their applicability to the combination setting.
- Although the use of a range of incremental QALY gains and ICERs was felt to be reasonable, this may be limited due to the confidentiality of the STA process and reporting that only occurs after the Committee's final decision. It was noted that this could become another factor in negotiations and that there may be a role for the HTA body throughout the discussion to provide indicative base-case QALY and ICER ranges and take a more active role.

2. <u>Pricing</u>

- Participants expressed interest in the principle of non-uniform pricing and its relevance to combination treatments, particularly given the competition law considerations posed by uniform pricing described in the Voluntary Arbitration Whitepaper. NHS England's Commercial Framework's potential consideration of non-uniform pricing in relation to an agreed combination treatment solution was noted in the discussion.
- The issue of confidentiality in HTA submissions was raised as a potential barrier to implementation, as ICERs and QALY gains are often redacted in HTA submissions to protect the confidentiality of discounts:
    - Participants noted that the issue of confidential pricing could apply to both the treatments under appraisal and comparators.
    - Takeda clarified that the proposed Value Attribution Framework was intended to rely only on QALYs, and not ICERS or confidential prices and that the use of

external clean teams was intended to allow discussion of confidential information without dissemination to the wider businesses.
    - It was suggested that HTA agencies might have a role in the negotiation process to address the challenge of confidentiality. However, the capacity and resource constraints of the HTA body would need to be taken into consideration.
    - Members of the Advisory Group noted that, although the proposed solution was intended to minimise the burden on HTA bodies and the NHS, there was no opposition to their involvement if required. However, it would be for NICE and other HTA bodies to comment on the appropriate level of involvement.

3. <u>Voluntary Arbitration Framework</u>

- Although the Value Attribution Framework was received positively, participants expressed the view that agreement on relative value will always come down to a negotiation between companies with vested interests and strategies. It is therefore important that all stakeholders accept responsibility to contribute to a solution.
- Participants stated that having a laid-out framework, such as the Value Attribution Framework, on which to base a negotiation process is helpful and provides a good starting point.
- Participants agreed with the principle of mandatory engagement with the process but the voluntary implementation of the outcome.
- It was suggested that, although market share provides a starting point for the definition of market power, other relevant factors should also be considered, including the size of the company, patent length and the relative importance of the product launch to the company (i.e., within the context of a large portfolio with many product launches, or few assets and a streamlined pipeline).
- A range of views were expressed on the incentives for backbone and add-on manufacturers to commit to negotiations and whether the Framework fully addresses this issue. However, it was noted that there is already a significant imbalance in incentives, with no requirement for backbone manufacturers to negotiate and the entire investment borne by the add-on manufacturer.
    - There was concern that the add-on manufacturer would be committed through investment in the HTA process and negotiations and that the process could collapse if the company providing the backbone treatment were to withdraw from negotiations.
    - It was noted that UK teams within companies could face challenges to secure the necessary investment to submit a dossier from global and regional levels, particularly when there is uncertainty surrounding the outcome of HTAs. Therefore, processes that introduce uncertainties, or have the potential to reduce the likelihood of positive reimbursement decisions, may have a detrimental effect on internal decisions to submit to HTA bodies.
    - It was also recognised that the backbone manufacturer might often have greater negotiating power, as most scenarios are likely to involve imperfect information.
    - However, it was noted that the balance of power may not always be in favour of the backbone manufacturer, given the incentive of increased duration of treatment, which may offset any reduction in the price of the backbone treatment.
    - It was suggested that earlier engagement with the backbone manufacturer could be helpful, particularly as there may be a disproportionate impact on some companies, such as those in oncology.

- It was suggested that the long-term success of the Framework would be dependent on how companies view repeated engagement in negotiations and the reputational effect of withdrawing.
- Whilst the Value Attribution Framework was deemed to be simple to implement, the group expressed some concerns over the practicality of the Voluntary Arbitration Framework from the perspective of HTA bodies, given the potential to add complexity to an already complex process.
    - Participants noted that negotiations might be resource-intensive, with the potential for multiple rounds of negotiation. Although initial rounds may be company-to-company, participants considered it potentially inevitable that HTA bodies and or payers would need to become involved in negotiations.
    - Scalability and the potential to prolong the HTA process were highlighted as possible challenges due to the potential for multiple concurrent combination appraisals, each requiring interaction with HTA bodies and payers. Takeda clarified that the Voluntary Arbitration Framework proposes that a 'Terms of Engagement' outlining the parameters for engagement could be agreed upon by all parties in advance of the process commencing. The Arbitrator could leverage the Terms of Engagement to ensure that negotiations reach a timely conclusion.
    - Takeda noted that the process was front-loaded to minimise the disruption and potential delay to the NICE STA process and that in publishing the Framework, it was hoped that others could provide feedback and suggestions to address any bottlenecks in the process.
    - Participants agreed with the principle of 'front loading' discussions to reach an agreement on as many aspects as possible before entering the formal HTA process. However, the likelihood of multiple touchpoints or cycles of negotiations throughout the STA process was envisaged due to the changes in assumptions during the appraisal. Participants felt that there might be a role for NICE and NHS England to play in informing these rounds of discussions
    - It was suggested that the initial value attribution might not need clean teams, and instead, HTA bodies could calculate a starting point for negotiation.

4. <u>Comparison with alternative solutions in development</u>

- Based on comments from attendees familiar with the current ABPI proposal, it was noted that the ABPI methodology and Takeda's proposed Framework take a different approach.
- The importance of collaboration with the ABPI pilot was stressed, and the outcome of this process would be very informative to moving forward in resolving this issue.
- It was noted that Takeda's proposed solution shares some conceptual similarities with the Office of Health Economics consulting report, *Why we need a new Outcomes-based Value Attribution Framework for Combination Regimens in Oncology,* commissioned and funded by Amgen.[5]
- There was agreement that all proposed solutions add to the tapestry of options to resolve this long-standing issue, and the group noted that the ABPI is best placed to deliver a package of solutions.
- Participants applauded the recent efforts from stakeholders to address this issue and called for all interested parties to now take an active role in moving from theory to implementation of a solution; *"it is now time for all actors in the system to take their part in solving this problem".*

6. Agreed actions and next steps

The Chair closed the meeting by summarising the key themes of discussion that arose during the meeting and stressed that Takeda is committed to further discussing these important topics. Helen Taylor (Programme Realisation Manager, Takeda) then briefly outlined Takeda's planned next steps.

Next steps

Ms Taylor noted that further feedback from those in attendance is welcome to allow refinement of Takeda's proposals and that continued discussion following the outputs of other workstreams in this area would be valuable.

Roundtables have also been completed with the clinical, patient, and legal communities; materials developed throughout Takeda's stakeholder discussions, including this summary report, will be accessible on the Takeda UK website: https://www.takeda.com/en-gb/what-we-do/combination-treatments/.

In early 2022, a summary report will be produced, covering the key areas for further discussion raised in all four Roundtable meetings.

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References

1. Briggs AH, Doyle A, Schneider J, et al. *An Attribution of Value Framework for Combination Therapies*. 2021. https://www.takeda.com/49a844/siteassets/en-gb/home/what-we-do/combination-treatments/a-value-attribution-framework-for-combination-therapies-takeda-whitepaper.pdf
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3. Davis S. *Assessing Technologies that are Not Cost-Effective at Zero Price*. 2014.
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5. Towse A, Lothgren M, Steuten L, et al. *Why we Need a New Outcomes-based Value Attribution Framework for Combination Regimens in Oncology*. 2021.

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