Overcoming the Combination Treatments Challenge: It's all about the Implementation

Chaired by Meindert Boysen

Tuesday, 25th March 2025, held virtually

Virtual expert panel discussion Report

Introduction

This Report summarises a virtual panel event on overcoming the access challenges to combination treatments, focusing on how any solution could be implemented and what still needs to be done. The event was hosted online by Takeda UK Ltd. and took place on Tuesday, 25th March 2025.

The Report should not be considered a consensus document; it is a balanced reflection of the virtual expert panel discussion during the event.

The panel have been given the opportunity to comment on this Report, which has been produced by Takeda and Red Thread Market Access.

Panel speakers:

- Meindert Boysen (Chair): Independent HTA expert.
- Emma Roffe (Panellist): Oncology Country Head (UK & Ireland) at Takeda UK Ltd.
- Shelagh McKinlay (Panellist): Director of Research and Advocacy, Myeloma UK.
- Professor Martin Kaiser (Panellist): Chair of Haematology and Consultant Haematologist at the Royal Marsden and Clinician Scientist at the Institute of Cancer Research.

Audience:

The audience comprised key stakeholders from across the policy, payer, patient group, media, academic, clinical and pharmaceutical industry communities.

Purpose

Takeda has a history of collaborating with stakeholders to solve complex challenges that enhance patient access to innovative treatments. It was therefore natural for Takeda to take on the challenge of combination treatments. To date, Takeda, in collaboration with stakeholders, has published two Whitepapers (2021), which have been reviewed and critiqued in a series of roundtables,[1,2] and led to the publication of two papers in 'Value in Health'.[3,4] To further address the cost-effectiveness challenges for combination treatments, Takeda has developed a Conceptual Implementation Framework; Making Solutions Transactable for Combination Treatments in a Not Cost-Effective at Zero Price Scenario.[5]

With the UK government and National Health Service (NHS) England now also considering the issue (Competition and Markets Authority [CMA] prioritisation statement, voluntary scheme for branded medicines pricing, access and growth [VPAG] commitment, and consultations on the NHS Commercial Framework),[6–8] the time seemed right to highlight the issue to a broader range of stakeholders.

In March 2025, Takeda UK held a virtual expert panel discussion *'Overcoming the Combination Treatments Challenge: It's all about the Implementation'.* The aim was to

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introduce the continuing challenge surrounding patient access to combination therapies and given all the work completed to date, what else in regard to implementation work is still needed, to ensure patients can benefit from the potential of combination treatments as rapidly as possible.

This document is a Summary Report of the insights from the virtual expert panel event highlighting the common themes and differences.

The event covered:

- Relevance of the combination treatments discussion now.
- Summary of the progress that has been made in recent years.
- Discussion on the challenges to accessing combination treatments.
- Discussion on the possible solutions for accessing combination treatments.

Summary of key discussion points

- Challenges associated with accessing combination treatments remain, and until they are addressed, UK patients remain unable to access potentially beneficial treatments.
- Positive steps have been made towards finding a workable solution, by Takeda and other stakeholders, but more must be done.
- Considering recent guidance from the UK government and NHS England alongside work done by Takeda to develop a Conceptual Implementation Framework, the time is right to bring this discussion to a wider range of stakeholders.
- The 'not cost-effective at zero price' and 'value attribution' challenges can be exacerbated by the default position of treating patients to progression as well as trial designs that fail to capture the value of combination treatments. However, limited treatment duration can have negative consequences regarding clinical outcomes and amendments to trial design may not be realistic in the context of global clinical trials.
- The most workable solution to solving the combination treatments challenge will come from flexible payment and pricing mechanisms, which have already been touched upon in recent UK government and NHS England guidance:
  - CMA prioritisation statement.[6]
  - VPAG commitment.[7]
  - NHS England Commercial Framework.[8]
- Overall, panellists felt that all stakeholders deserve recognition for their efforts in this field, but achieving a solution will require collaboration from all parties involved. Flexibility and pragmatism are essential, with a focus on the broader benefits for patients, the healthcare system, payers, and industry. Ultimately, the goal is to provide access for patients to effective treatments.

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Detailed Report of the virtual expert panel discussion

1. Introduction from the Chair for why a Conceptual Implementation Framework is needed now

Meindert Boysen (independent HTA expert) introduced the aims of the virtual expert panel discussion and invited the panellists to introduce themselves. He provided attendees with an overview of the relevance of the discussion to today and a summary of the key challenges that would be examined in further detail throughout the event.

During his introduction, Mr Boysen outlined that:

- Combination treatments combine two or more individual drugs, comprising a backbone treatment (either a single treatment or an existing combination) and an add-on treatment.
- Accessing combination treatments remains a significant challenge:
  - In some cases, they would not be cost-effective to fund even if the new drug was given away for free ('not cost-effective at zero price'). Often, this is due to improved efficacy, resulting in longer treatment and higher costs.
  - Combination treatments are normally commercialised by different companies, and anti-competition law means these companies can't discuss pricing together.
  - The value contributed by the different treatments in the combination, and the value of the combination treatment to the wider healthcare system can be difficult to determine.
- The inability of patients to be able to access combination treatments is a critical issue that needs to be solved *today*. According to the Association of the British Pharmaceutical Industry (ABPI), half of their members' oncology pipelines are combination therapies.[9]
- There are two key reasons for why this has become such a prominent topic:
  - Our understanding of disease biology has improved and we are now aware of multiple drug targets and therefore multiple ways to address a disease. There is a need for combination treatments to overcome increasing cell resistance.
  - Since 2017, the number of combinations treatment trials has increased significantly. In 2017, 70% of trials were for monotherapies, while in 2021 this decreased to 20–30%.[10]
- Positive steps have been made towards finding a solution, but more must be done, and this will require collaboration from all stakeholders involved.
- Building on Mr. Boysen's remarks, Professor Kaiser and Ms. McKinlay emphasized the urgent need for access to combination treatments. This necessity is crucial both for clinicians in effectively managing patient care and for patients, who benefit from the reassurance of having viable treatment options readily available when required.

2. Progress made towards combination treatment access

To open the discussion on the continued challenges and potential solutions, Meindert invited Emma Roffe (Oncology Country Head [UK & Ireland] at Takeda UK Ltd) to present the work done to-date on the combination treatments challenge.

Dr Roffe described the following actions:

- In 2014, a report by the National Institute for Health and Care Excellence (NICE) Decision Support Unit highlighted the 'not cost-effective at zero price' challenge for combination treatments, where a highly effective combination treatment could fail to meet cost-effectiveness thresholds even when the add-on was provided at zero price. Despite discussions, no action was taken.
- Takeda took initiative in 2017 to unite stakeholders – including academics, health economists, patient advocates, legal experts, NHS England and NICE – to develop solutions. This led to the publication of two White Papers in 2021:
  - Attribution of Value Framework for Combination Therapies: Proposed a method to assign relative value to each treatment in a combination.[1]
  - Voluntary Arbitration Framework for Combination Therapies: Suggested a process for commercial discussions between competing companies.[2]
- These White Papers, while not definitive solutions in themselves, provided a foundation for further work, and were reviewed and critiqued by all interested stakeholders. In January 2025, two articles based on the findings of these White Papers were published in Value in Health:
  - Briggs, Andrew H. et al. An Attribution of Value Framework for Combination Treatments. Value in Health, Volume 28, Issue 1, 72 – 80.[3]
  - Steuten, Lotte et al. Proposal for a General Outcome-Based Value Attribution Framework for Combination Therapies. Value in Health, Volume 28, Issue 1, 81 – 87.[4]
- In recent years, momentum has grown elsewhere:
  - The CMA issued a position statement allowing competing companies to collaborate on a commercial agreement without fear of investigation in this specific circumstance.[6]
  - The 2024 VPAG included commitments to support implementation of solutions.[7]
  - Ongoing consultations on the NHS England Commercial Framework have reflected on the CMA prioritisation statement and VPAG commitments on combination treatments and consider options for transacting workable solutions.[8]
- Takeda have now developed a Combination Treatment Conceptual Implementation Framework that:
  - Explores how we can utilise and evolve existing processes.
  - Outlines the critical points in the process for involvement of stakeholders and decision makers to highlight cost-effectiveness issues and discuss solutions early.
  - Helps flag and resolve issues ahead of HTA.
  - Promotes collaboration among all stakeholders.[5]

3. Exploring the challenges surrounding access to combination treatments

The discussion around 'challenges surrounding access to combination treatments', was a largely open discussion from the panellists, voicing their thoughts and experiences in this area. To facilitate the panel discussion, Meindert Boysen summarised his own thoughts and asked questions throughout, based on the flow of conversion. For this Report, these discussions have been grouped together into themes, and as such the discussion points do not necessarily reflect the chronological flow of conversation during the virtual panel event.

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While the points below are reflective of at least one of the panellists, they may not be reflective of all their views.

Building on the discussion around 'not cost-effective at zero price' and 'value attribution', Mr Boysen asked some further questions to investigate the challenges surrounding access to combination treatments further.

Mr Boysen noted that one of the fundamental issues contributing to the 'not cost-effective at zero price' challenge, is that we are treating patients for longer with the backbone therapy. Could this issue be solved if we stopped treatment before progression?

Professor Kaiser and Ms McKinlay agreed that:

- Provided the evidence shows that limited treatment duration yields the same outcomes as ongoing treatment, it benefits both patients and the healthcare system to not treat to progression (reduces costs and improves patient quality of life).

However, Professor Kaiser noted that:

- Pricing can be structured to ensure time-limited treatments still generate revenue.
- For genetically diverse disease like multiple myeloma (MM), ongoing treatment with certain drug classes has proven beneficial for progression-free and overall survival.
- As treatments evolve, new drug classes may allow for limited-duration therapies, but long-term maintenance will likely remain essential in some disease areas.

Mr Boysen pushed this discussion further, asking if it would be possible to enforce a limit on the treatment duration of one of the drugs in the combination e.g. the backbone when you would otherwise have stopped it?

Professor Kaiser explained that:

- There are trade-offs between accessibility and outcomes. Several trials in MM have explored stopping one of the treatments before progression. This has made the combination treatment more immediately accessible, but led to weaker long-term efficacy.
- Current evidence shows a clear decline in outcomes when one drug in a combination is discontinued, especially in an incurable, remitting, relapsing, and very heterogenous disease like MM.

Mr Boysen introduced clinical trial design as a topic, noting how there are no trials of combination vs. backbone therapy. He asked if the issue was with the evidence? Are we not able to properly attribute clinical effect of the addition because we don't design the right trials?

Professor Kaiser and Ms McKinlay contributed the following discussion points:

- Clinical trial design could be improved to better capture the value of combination treatments and demonstrate patient benefits.
    - This is becoming more feasible with combinations involving four drugs, as seen in a recent academic study (supported by industry) that investigated a different arrangement of the four drugs (as backbone vs add-on) than the registrational trial, demonstrating a similar efficacy contribution from all components.
    - Trials assessing the value of the individual treatment components are less constrained than registrational trials, and could be conducted by academic partners.

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- Some benefits of combination treatments are often overlooked and hard to reflect, such as:
  - Tolerability: In the event of side effects, the dose of one component in the combination can be adjusted, while maintaining the benefits from the full dose of the other treatment(s). Allowing, to some extent, individualised patient care.
  - Value of remission: In MM, the health state a person is living in while in remission contributes to the 'not cost-effective at zero price' challenge. The value of this, particularly to patients, could be better captured.

Dr Roffe provided some insight from an industry perspective:

- Modifying trial design is complex, and while valid, may not be realistic. Cost-effectiveness is a priority only in some markets (UK, Australia, Ireland, Canada and Sweden), and most industry-sponsored registrational trials are global, following international standards.
- Mr Boysen agreed, stating the solution cannot rely solely on industry. Public sector investment in knowledge gathering is needed.

Mr Boysen mentioned a recent ABPI report which stated that almost 25% of non-submissions were from combination treatments unable to meet cost-effectiveness criteria. Is there an issue with an increasing number of non-submissions to NICE and consequent limitations in patient access?

Ms McKinlay noted that:

- While MM presents a 'success story', with many combination treatments available, many combination treatments never make it to NICE. Blood Cancer Alliance reviewed NICE appraisals over five years, and recently published a report revealing:[11]
  - Higher appraisal termination rates in blood cancer (38%) vs oncology (14%).
  - Blood cancers accounted for 60% of all terminated appraisals.
  - The most common reason given was that the drug was unlikely to be cost-effective.
- Resolving this issue requires collaboration among all stakeholders – NICE alone cannot solve it.

4. Potential actions stakeholders can take to find a solution to the combination treatments challenge

Meindert Boysen invited the panel speakers to discuss possible solutions to the challenges presented by combination treatments. He provided a brief narrative grouping possible solutions into three themes; clinical development and design, HTA process and finally flexible payment and pricing mechanisms. He then invited the panellists to discuss and offer their feedback on these solutions.

Theme 1: Clinical development and design

Mr Boysen referred to earlier discussions on this topic, where it was acknowledged that improvements could be made to better capture the value of combination treatments, but modifications to trial design were not always realistic in the light of global clinical trials. In a question targeted to Professor Kaiser, he asked whether drug delivery in a single molecule could provide the solution.

In response, Professor Kaiser explained that:

- ‘Combination treatments’ have certain clinical benefits, that cannot be achieved using single molecule drug delivery:
  - Treatment flexibility e.g., side effects can be mitigated by adjusting the dose of one treatment, but efficacy maintained due to normal doses of the other components.
  - Targeting of various disease mechanisms e.g. in MM; surface receptors, molecular glue degraders, broad targets e.g. metabolic drugs and steroids.
  - Complex and bespoke disease management in the absence of complex or bespoke treatment pathways e.g. for less common diseases with low patient numbers, like MM, where there is no clear treatment pathway, combination treatments enable clinicians to achieve the treatment individualisation available for other diseases (like breast cancer) that have complex treatment pathways.

<u>Theme 2: Increasing the HTA willingness to pay (WTP) threshold for combination treatments</u>

- Overall, panellists agreed that this was not a viable long-term solution.
- Dr Roffe mentioned that increasing the WTP threshold could help more combination therapies gain approval, but is not a definitive solution. A recent publication found that raising the threshold alone is not a ‘golden bullet’.
- Ms McKinlay highlighted that since disease areas, indications and technologies vary, the pricing gap can be quite substantial e.g. for a rare cancer treated with a highly specialised technology.
- Mr Boysen added how it would be unfair to assign greater value to combination treatments over monotherapy, without considering e.g., disease severity.

<u>Theme 3: Flexible payment and pricing mechanisms – negotiating a reduction in price of constituent parts of the combination</u>

- Panellists agreed that pricing flexibility and mechanisms provides the most promising solution.
- Dr Roffe mentioned how the recent CMA guidance on competition law has reassured industry that compliant pricing discussions between companies for components in a combination are possible.
- Ms McKinlay emphasised the importance of multi-indication pricing: While ‘uniform pricing’ remains the norm, the new NHS Commercial Framework outlines the possibility for multi-indication pricing. Enabling companies to price by indication, could allow them to be cost-effective for combination treatments, without impacting revenues across all indications. However:
  - Guidance for companies is crucial, to instil confidence when entering into these commercial discussions – this is why the recent CMA prioritisation statement, VPAG commitment and NHS England Commercial Framework are important.
  - Despite the guidance, there are still barriers to accessing flexible pricing e.g., requirements outlined in the NHS Commercial Framework.
  - The practical challenges of implementing multi-indication pricing from an NHS England perspective need to be explored.

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- Mr Boysen highlighted a paper by Adrian Towse that outlined four key issues in valuing and paying for combination therapies; incentives; value attribution, competition law and implementation. He stressed that 'value attribution' is essential, as without it, there's no incentive for discussion, and without that no relevance of competition law. Dr Roffe explained that while Takeda's White Papers,[1,2] and the resultant peer reviewed publications,[3,4] propose a solution, no-one is aware of any medicines that have gone through and utilised it in the process to test it.
- Mr Boysen raised the requirement that a product must be highly cost-effective (incremental cost-effectiveness ratio ≤ £20,000/Quality adjusted life year) to allow pricing flexibility. Dr Roffe acknowledged this *quid pro quo* requirement, emphasising the need for balance (pricing flexibility for industry whilst maintaining value for the taxpayer and covering additional costs for implementation).

5. Facilitated Q&A

After listening to the discussion by panellists on the challenges and possible solutions for combination treatments, the Chair opened the discussion to attendees.

Early combinations that we've seen are using backbone therapy that's relatively old, and therefore the patent life for that technology is probably expiring. There may not be a big incentive for these companies to then engage, which might be quite different if we have combinations of technologies that are all very early in their development. Is this a reasonable concern?

- This was a consideration when developing the initial White Papers – what's in it for the backbone company? The conclusion was that companies will alternate between being the backbone and the add-on, so sometimes will be 'winners' and other times 'losers'.
- Industry needs to see the 'bigger picture', understanding that at some point it will be their turn.

What are your opinions on the co-creation of clinical trials e.g. with patient organisations? Are we too narrow in our measures of benefit in current clinical trials? Should we be more interested in broader capturing of benefits post treatment or in progression-free survival?

- A lot of work is being done with patient organisations to better incorporate patient-reported outcomes in clinical trials. However, there are challenges:
  - Organisation of the different parties and generating interest/desire in this.
  - Approval.
  - Ability to compare results between trials – how to interpret and use/utilise the data that is gathered.
  - Funding.

6. Closing remarks

The Chair closed the event by inviting panellists to make any closing remarks:

The panellists agreed that while stakeholders deserve recognition for their efforts in this field, achieving a solution will require collaboration from all parties involved. Flexibility and pragmatism are essential, with a focus on the broader benefits for patients, the healthcare

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system, industry and payers. Greater public investment and awareness are needed to highlight the benefits of understanding disease, its natural history, and the added value of combination treatments – this can be driven by researchers and patients rather than the industry. Ultimately, the goal is to provide patients with effective treatments.

He then thanked the panellists and the audience for their attendance and closed the event.

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