



Solving the challenge of combination treatments: Takeda clinical roundtable on access to combination treatments in the UK

Wednesday 29 September 2021, 17:00-19:00, held virtually (MS Teams)

Meeting Report

Introduction

This report provides a summary of a clinical 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 Wednesday 29 September 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.

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

Attendee list

The following individuals and organisations were present during the meeting:

- Dr Claire Dearden, Consultant Haematologist (The Royal Marsden Hospital)
- Dr David Gilligan, Consultant Oncologist (Royal Papworth Hospital NHS Foundation Trust)
- Dr Graham Collins, Haematology Consultant (Oxford University Hospitals NHS Foundation Trust)
- Dr Josh Wright, Consultant Haematologist (Sheffield Teaching Hospitals NHS Foundation Trust)
- Dr Martin Foster, Consultant in Medical Oncology (University College London Hospitals NHS Foundation Trust)
- Dr Neil Rabin, Consultant Haematologist and Takeda Advisory Group member (University College London Hospitals NHS Foundation Trust)
- Dr Ruth Pettengell, Reader / Honorary Consultant in Haematology / Oncology (St George's University Hospitals NHS Foundation Trust)
- Ms Lisa Barrott, Macmillan Nurse & AHP lead for Cancer, Palliative & End of Life Care (University Hospitals Sussex NHS Foundation Trust)
- Professor Peter Taylor, Norman Collisson Chair of Musculoskeletal Sciences (University of Oxford)
- Eric Low [Chair], Independent Consultant and Chair of Takeda UK's Combination Treatments Advisory Group
- Danielle Smith, Head of Professional Relations and Patient Advocacy (Takeda UK)
- Helen Taylor, Programme Realisation Manager (Takeda UK)
- Jerome Penn, Senior Public Affairs Manager (Takeda UK)

Purpose

The purpose of the Roundtable was to consider combination treatment access challenges and to solicit feedback on a proposed solution developed by Takeda UK. Participants included clinical experts from across different therapy areas, to ensure the discussion represented and reflected a range of perspectives. It also aimed to identify the role clinicians could play in the potential operation of a solution and how Takeda UK could partner with the clinical community to ensure solutions are adopted.

The Roundtable covered the following:

- The challenges of patient access to combination treatments
- Takeda's approach to developing a solution
- Takeda's proposed solution
- Refining the proposed solution and gathering feedback
- Involvement of the clinical community in building advocacy for the proposed solution and in its operation
- Summary of actions and next steps

Takeda's approach to developing the solution and its components are contained within the two Whitepapers: [An Attribution of Value Framework for Combination Therapies Whitepaper](#) and the [Voluntary Arbitration Framework for Combination Treatments Whitepaper](#). Wider information on Takeda's proposal can be accessed on the Takeda website [here](#).

Summary of the key discussion points

The following discussion points are the highlights from the Roundtable. Further details around the discussions can be found later in the Report:

- Until the challenges associated with access to combination treatments are addressed, both now and in the future, patients may be unable to benefit from the potential of combination treatments due to delays in access or no access at all (*see chapter 1*)
- There is a need for a multi-stakeholder approach to a solution, that involves clinicians, patients, and the competition law community, as well as NICE (National Institute for Health and Care Excellence) and the pharmaceutical industry (*see chapter 1*)
- Takeda's proposed solution is one of several proposed solutions being developed by industry and other stakeholders (*see chapter 1*)
- It is important that any solution is aligned with existing NICE processes, and is future proofed for any changes to NICE or NHS England and NHS Improvement (NHSE-I) processes (*see chapter 2*)
- Takeda's proposed solution is made up of two component "Frameworks" that are intended to be used together: the Attribution of Value Framework (to attribute value to each treatment) and the Voluntary Arbitration Framework (to ensure compliance with competition law) (*see chapter 2*)
- Concern was raised as to whether NHSE-I would buy-in to the need for non-uniform pricing arrangements to be a part of the solution, though it is critical that these arrangements exist to ensure manufacturers are willing to participate in the process (*see chapter 3*)
- Whilst outside the scope of Takeda's proposed solution, it is important that future clinical trials are designed differently to capture the value of combination treatments more

effectively for Health Technology Assessment (HTA) and to deliver the clinical data necessary to demonstrate patient benefit

- Manufacturers must be clear on the incentives of adopting and agreeing to participate in the solution and / or be clear on the fact there is no disincentive to participation. It was also noted positive case studies will be needed to encourage manufacturers as to the value of the solution – which should then lead to higher uptake of it
- The clinical community can play a key role in advocating for the implementation of a solution; by speaking collectively on behalf of their patients and in collaboration with the patient advocacy community to highlight the challenges posed by combination treatments, the impact on patient access and the need to identify a solution (*see chapter 4*)

Detailed report of the Roundtable

1. The challenges posed by combination treatments: a presentation by Eric Low and Neil Rabin

To introduce the Roundtable, Eric Low (Independent Consultant and Chair of Takeda UK's Combination Treatments Advisory Group) and Dr Neil Rabin (Consultant Haematologist and Takeda Advisory Group member) were invited to present their perspectives on the challenges presented by combination treatments. The views expressed below are those of Mr Low and Dr Rabin, and not necessarily representative of all participants.

During Eric Low and Dr Neil Rabin's presentation, they outlined that:

- Combination treatments are becoming increasingly common as the understanding of complex diseases increases, and there is acknowledgement that they can lead to improved patient outcomes, survival, and quality of life
- They are currently most common in oncology, where there are a number of promising combination treatments already available. However, delivering patient access to these treatments presents a challenge to HTA systems as they often face cost-effectiveness barriers even if the new add-on treatment were to be given away at zero price
- Whilst there are currently fewer examples outside of cancer of the access challenges presented by combination treatments, there are likely to be similar issues in many other disease areas, including rare diseases like cystic fibrosis
- There is therefore consensus within key stakeholder groups, nationally and internationally, that solutions for accessing combination treatments need to be quickly found for the benefit of patient outcomes, now and in the future
- This challenge is not new and was identified by the NICE Decision Support Unit in 2014, prompted by a technology appraisal in metastatic breast cancer
- Since this report, work to assess and resolve the challenges presented by combination treatments has accelerated
- Takeda recognised that there was a need to develop a solution and worked in partnership with the patient, clinical, academic and competition law communities to develop a solution that represents the perspectives of multi-stakeholders. Representatives from NICE and NHS England provided feedback on key challenges
- The Government has assigned the Association of the British Pharmaceutical Industry (ABPI) with responsibility for developing a solution to the challenge of combination treatments, and Takeda is working closely with the ABPI in support of this ambition

2. Takeda's approach to finding a solution: a presentation by Helen Taylor

Helen Taylor (Programme Realisation Manager, Takeda UK) provided attendees with an overview of the background to Takeda's proposed solution, including the multi-stakeholder work that has underpinned its development so far, and the rationale behind Takeda's approach and philosophy.

During her presentation, Ms Taylor highlighted the following:

- Takeda has been looking into the challenges posed by combination treatments since 2016 and there is international consensus that a fair, implementable and transactable solution

needs to be found – as shown in concurrent work being developed by other interested parties

- With input and advice from an Advisory Group of experts from legal, economic, academic, patient and clinical communities, Takeda has developed two Whitepapers setting out a proposed solution for improving access to combination treatments – and the two distinct Frameworks that make up the solution are intended to be used together:

1. Attribution of Value Framework

The Attribution of Value Framework proposes an economic methodology that 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 health benefit. It takes into consideration the health-economic methods used by NICE in making decisions about access to medicines.

2. Voluntary Arbitration Framework

The Voluntary Arbitration Framework proposes a standard operating procedure to support compliant dialogue and agreement between pharmaceutical companies on the value attributed to each treatment within a combination. It takes into consideration competition law and the current NICE processes in making decisions on access to medicines.

- The two Frameworks were developed based on a series of key requirements that the Advisory Group identified which a solution must satisfy. These were:
 - Deliver improved patient access to combination treatments
 - Be compatible with the existing NHS England Commercial Framework and NICE methods and processes
 - Adhere to existing cost-effectiveness thresholds
 - Address competition law issues
 - Encourage manufacturers to work together
- The methodology of the Attribution of Value Framework allocates a proportion of the value between the treatments in a combination; with value defined as the quality-adjusted life year (QALY) gain which is based on clinical trial data. It considers four scenarios:
 - Perfect and imperfect information
 - Same & different manufacturers
- The Voluntary Arbitration Framework was developed in line with the current NICE STA process and consists of the following four elements:
 - 'Clean teams'
 - Non-uniform pricing
 - A long-term commitment to participate
 - The option of adjudicator oversight
- The solution has been developed in accordance with current NHSE-I commercial and NICE methods and processes and is intended to be flexible enough to adapt to any future changes to NICE or NHSE-I processes (e.g., the new NHS England Commercial Framework and potential changes adopted through the NICE methods and processes review)

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 Treatments* Whitepaper and the *Voluntary Arbitration Framework for Combination Treatments* Whitepaper.

3. Refining the proposals and gathering feedback: group discussion

After listening to the presentations on the cost-effectiveness and competition law challenges associated with combination treatments, Takeda's approach to developing a solution and the key elements that comprise Takeda's proposed solution, the Chair opened the discussion to attendees. Specifically, he asked attendees to provide their reflections on the principles and concepts underpinning the solution, as well as how it could be applied within the context of the NICE HTA process.

Overall, participants welcomed Takeda's commitment to driving the agenda by putting forward a potential solution. However, they also posed a series of questions and challenges. Takeda representatives answered and provided clarity on these questions and challenges and noted that Takeda is committed to working collaboratively with all relevant stakeholders to find a solution. The questions and challenges discussed can be broadly split into the following key themes:

Non-uniform pricing

- Participants discussed the assumption of the Voluntary Arbitration Framework that payers will allow non-uniform pricing for the component treatments in a combination, and whether this would be accepted by NICE as part of the solution
 - Takeda responded that non-uniform pricing is already used in certain situations, such as for treatments approved via the Cancer Drugs Fund (CDF), where different pricing is used to indications that have baseline commissioning. It was noted NHSE-I has been clear there has to be a clear rationale to agree to non-uniform pricing in an appraisal, as per its Commercial Framework. Given this, it was stated that combination treatments are likely to fall within this rationale
 - It was added that at the outset of this work, Takeda ensured that a consensus on the problem posed by combination treatments was discussed with NICE and NHSE-I, and the need for non-uniform pricing arrangements to be a part of the solution was developed in response to this problem statement

Clinical trial design

- Participants discussed whether future clinical trials could be designed differently to capture the value of combination treatments more effectively for HTA and to deliver the data necessary to demonstrate patient benefit
 - Takeda recognised the challenge associated with clinical trial design and responded that whilst discussions on this issue had been held as part of the Advisory Group, this does not form part of this proposed solution – with the focus on solving the HTA challenge of combination treatments. This is because clinical trial design is a global issue that will take a concerted international approach, which realistically can only be achieved over a longer period of time. Takeda's proposed solution is intended to improve the availability of combination treatments in the short and medium term whilst change is affected earlier in clinical development programmes

- Once the HTA challenges have been resolved, it was noted that a focus will need to turn to improving clinical trial design and data inputs into HTA for combination treatments. The role academic networks can play in designing hybrid clinical trial studies in future should also be considered

Handling imperfect information

- Participants discussed the concept of handling imperfect information that forms part of the Attribution of Value Whitepaper, typically arising when a novel add-on is combined with an existing backbone treatment and where the independent benefit of one or more of the component treatments is unknown for the indication under consideration
- It was raised that attributing value from trial data of different treatments, based on different patient populations, was likely to be extremely difficult. Also challenging when assigning value to a component treatment is where its effectiveness in combination with a backbone is far superior to its use as a monotherapy
 - Takeda noted its proposed solution includes a formula that is designed to attribute value even where imperfect information exists and the inclusion of compliant intra-manufacturer discussions via the adjudicator and 'clean teams' offers an avenue to enable manufacturers to reach consensus on the distribution of value before submitting to NICE
- The possibility of using real-world evidence to supplement trial data and reduce the challenge posed by imperfect data was discussed by the group. It was agreed that while real-world evidence would be important for tracking patient outcomes, in most cases it would not be available at the time of the value attribution

Delaying patient access

- Participants expressed concern at the possibility that Takeda's proposed solution could add further time to the NICE process and subsequently impede patient access
 - Takeda responded that not all combination treatments will require the utilisation of the solution as it will only be used when it is clear that a treatment may face HTA challenges. It was noted that it would be for the adjudicator to decide a genuine candidate for the solution, which has been designed to mirror and interact with the existing NICE process so that timelines are not substantially delayed
 - Takeda also highlighted that HTA processes for combination treatments can often already be substantially longer than that of monotherapies due to existing cost-effectiveness challenges (if they are recommended at all). Therefore, delays caused by these challenges would hopefully be mitigated by the implementation of Takeda's proposed solution

Encouraging participation from manufacturers

- Participants also discussed the possibility that a company may be reluctant to enter into an agreement due to concerns that it could affect revenue in other indications, and questioned companies' willingness to participate if their monotherapy is subsequently valued less highly as a result of participating in the process. As a result, it was suggested that manufacturers will need to be clear on the incentives for participating in the solution, as well as being clear that there will be no disincentive. It was also noted that positive case studies will be needed to encourage manufacturers as to the value of the solution – which should then lead to higher uptake of it

- Takeda highlighted the importance of non-uniform pricing, which would ensure the value assigned to a treatment when used in a combination would not affect its value as a monotherapy in other indications. It was also noted discussions through ‘clean teams’ would be confidential, and any resulting commercial discussions with NHSE-I would remain confidential meaning the attribution of value would not be made public. It is hoped this will provide reassurance to manufacturers and encourage them to come to the table
- Participants enquired as to whether the increased cost of utilising the proposed solution and the associated ‘clean teams’ for a combination treatment could discourage companies from participating in the solution
 - Takeda responded that, as a proportion of the costs required to complete a NICE submission, the costs of employing ‘clean teams’ will be relatively minor. However, it was noted that these costs could be a factor in rare diseases and for small manufacturers. Takeda highlighted how the concept of ‘clean teams’ was deliberately designed to manage costs and that the criteria of a ‘clean team’ could be met by market access consultancies / agencies for example, rather than by competition lawyers
- Takeda also proposes that any solutions implemented to address the combination treatment challenge becomes embedded into the next Voluntary scheme for branded medicines pricing and access (VPAS), to encourage universal participation of the pharmaceutical industry, the NHS, and the wider healthcare community

Securing adoption of Takeda’s proposed solution and future evolution

- A question regarding the feasibility of securing the introduction of the solution, and subsequently who would be responsible for affecting and approving changes to the arbitration process, was posed
 - Takeda responded that the issues posed by combination treatments have already been recognised by the Department of Health and Social Care (DHSC) and are included in the current VPAS – so the expectation is that decision-makers are open to adopting a solution
 - It was also noted that the Advisory Group received input from NICE and NHSE-I on the challenges that exist, to ensure the solution meets the needs of current NICE processes and NHSE-I commercial methods
 - However, it was also accepted that there is a degree of uncertainty as to how the system may respond to the implementation of the solution. The group agreed it is important the model is tested so that success and positive case studies can be demonstrated to achieve buy-in of wider stakeholders. The solution may therefore be subject to iterative updates once implemented to ensure it operates optimally and maintains relevance in a changing environment

Securing international involvement in the solution

- Participants enquired as to the attitudes of pharmaceutical companies globally towards the cost-effectiveness challenges posed by combination treatments in certain market archetypes and whether the combination treatment access challenge is solely a UK issue to solve
 - Takeda highlighted how there is a global awareness of the need to tackle the issue of access to combination treatments and that this is not just an issue facing markets

- that adopt a cost-effectiveness HTA model. It was noted that in future we may see quintuplet combinations which has increased the traction of the issue, as even insurance-backed markets are likely to struggle to reimburse these treatments. Moreover, as NICE decisions are often referenced by other HTA systems globally, there is an interest in addressing the challenge in England as this can be influential for patient access in other countries
- The international workshop convened by the Bellberry Group and the work underway from the European Federation of Pharmaceutical Industries and Associations (EFPIA) were raised to demonstrate that this issue is being explored internationally

4. Takeda's engagement strategy and involvement of the clinical community in the solution: a presentation by Danielle Smith and group discussion

The Chair opened a group discussion and participants were invited to provide feedback on Takeda's approach to engagement, particularly around the role clinicians could play in the operation of the solution and how they can build support for it across the system.

The Chair noted that Takeda's engagement strategy aims to build awareness of the combination treatment challenge and generate platforms for discussion and debate to secure critical feedback on the proposed solution. Takeda also noted their intention to employ a considered and targeted approach to stakeholder engagement to secure support and action for solutions to be implemented.

- Participants discussed the role clinicians could play in the operation of a solution. In particular, it was noted that clinicians could support in horizon scanning through the early identification of combination treatments and potential access problems, the contribution of real-world evidence in handling imperfect information and in helping companies understand the broader meaning of value
 - In relation to horizon scanning, it was briefly considered that there is an opportunity for clinicians to signal which treatments might be eligible candidates to utilise the combination treatment framework. However, it was highlighted that decisions to take medicines through HTA are ultimately driven by the strategy and commercial objectives of the pharmaceutical company
 - On real-world evidence, the group agreed that if relevant data is already available then it has potential benefits in the attribution of value. However, it was cautioned that in the absence of relevant evidence at the time of consideration for HTA, the development of new data is too time consuming to be feasibly incorporated into the decision-making. There was also caution around mandating the accrual of real-world evidence as part of the process. Instead, it was proposed that there should be a way of incorporating the real-world experience of patients in the process
 - Participants queried whether the toxicity profile and associated service impact of a combination treatment was factored into the attribution of value, as well as other factors that demonstrate value outside of the clinical data plugged into a health economic model, e.g., true quality of life impact including psychosocial and broader economy implications. It was suggested that there could be a role for clinicians to advise on the broader meaning of value in this context
- Participants then discussed the role clinicians could play in building advocacy for the adoption of the solution

- Despite welcoming being involved in advocating for a solution, there was some debate about the influence of the clinical community in the HTA environment. However, the importance of the clinical community was highlighted in continuing to signal the impact of the problem posed by combination treatments on patient care and the need for a workable solution. It was agreed further discussions as to how clinicians can amplify their role and influence in the HTA process, and broader medicines access challenges, would be important
- There was consensus that the clinical voice is most powerful when spoken collectively and with a united voice with patient groups and the patients they represent. It was highlighted that it would be critical for the patient voice to be heard throughout the process – from the existing unmet need to the design and the prioritisation of research, and throughout HTA processes and the operation of Takeda's proposed solution

4. Agreed actions and next steps

The Chair closed the meeting by summarising the key themes of discussion that arose during the meeting and outlining Takeda's planned next steps.

Next steps

The Chair noted that further feedback from those in attendance would be welcome throughout 2021 and beyond.

Now the Voluntary Arbitration Whitepaper has been published, a link will be shared with clinicians in attendance and continued engagement with interested parties will also take place throughout the year. Attendees were asked to inform Takeda if they wished to continue to engage on the proposed solution.

In early 2022, all feedback from across Takeda's stakeholder discussions will be reviewed and, if deemed necessary, there is the potential to publish an addendum to the proposed solution that incorporates the proposed feedback captured during the roundtable discussions. Takeda wishes to encourage feedback, critique, and debate of the proposed solution in order to meaningfully present an implementable and transactable solution that represents perspectives from all stakeholders.

Materials developed throughout Takeda's stakeholder discussions, including this summary report, will be made accessible on the Takeda UK website: <https://www.takeda.com/en-gb/what-we-do/combination-treatments/>.