Combination Treatments – Value Attribution Summary

Better Health, Brighter Future

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What are combination treatments?

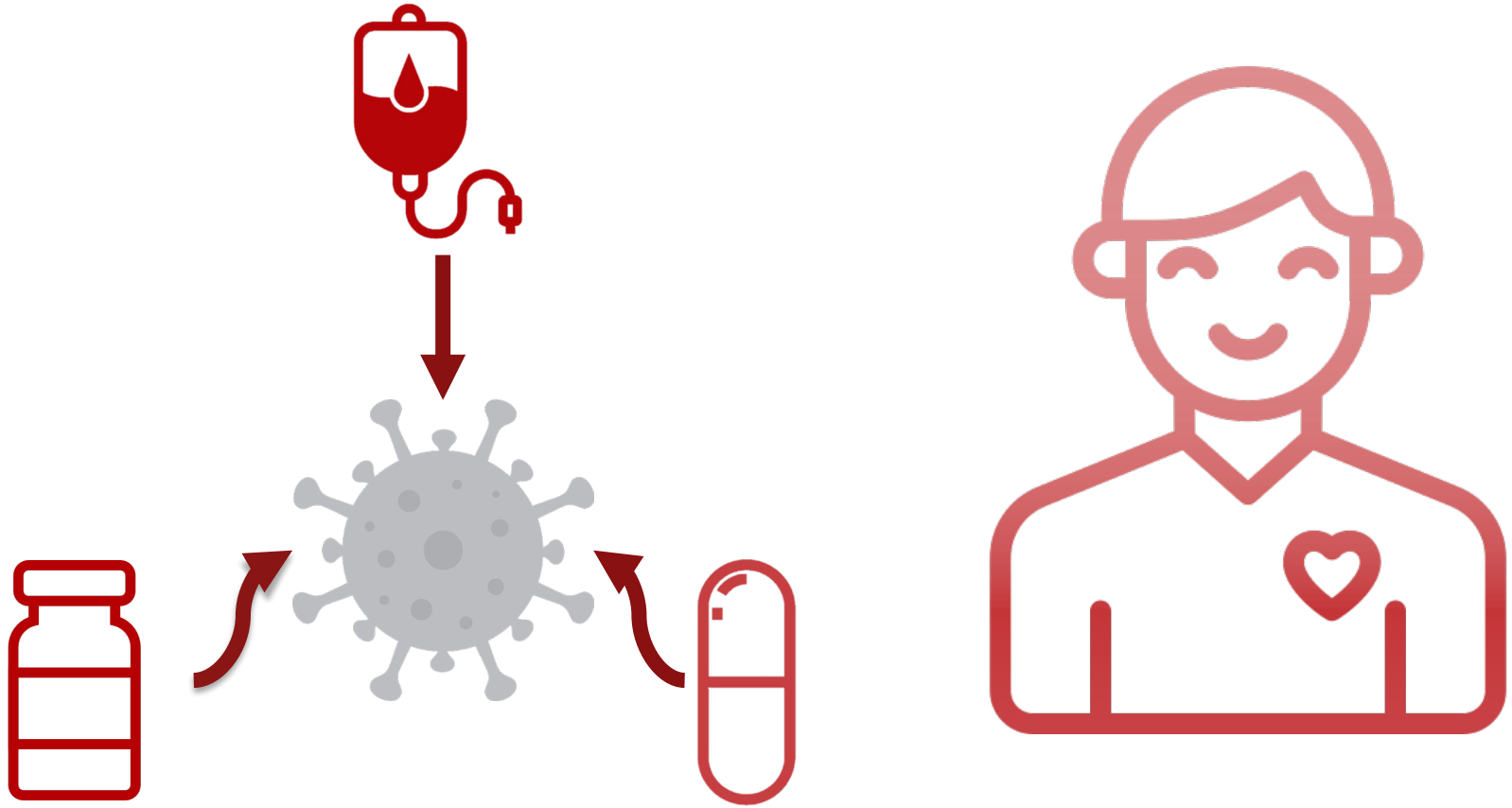
Combination treatments combine two or more individual treatments.

Many combination treatments combine a “backbone” treatment with a new “add-on” treatment. The backbone treatment is usually already available to patients and is generally considered to be standard of care.

The add on treatment is a new treatment, or treatments, that is added onto the existing backbone treatments and is given jointly as part of one treatment regimen. This is what we would term combination treatments.

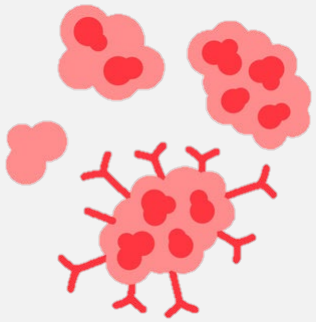
Why are combination treatments so important

Combination treatments have the potential to deliver significant health benefits to patients. This is because using multiple treatments in combination can simultaneously target numerous pathways that drive a disease.

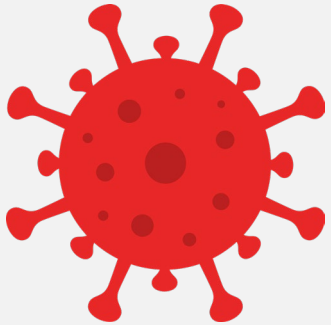


Where are combination treatments being used?

As the understanding of complex diseases increases, combination treatments are becoming more common. They have emerged as mainstay treatments in cancer. Treatment with multiple agents often generates a higher therapeutic response and better outcomes for cancer patients. However, combination treatments are not just restricted to oncology, as they can be used in a broad spectrum of disease areas.



Cancer



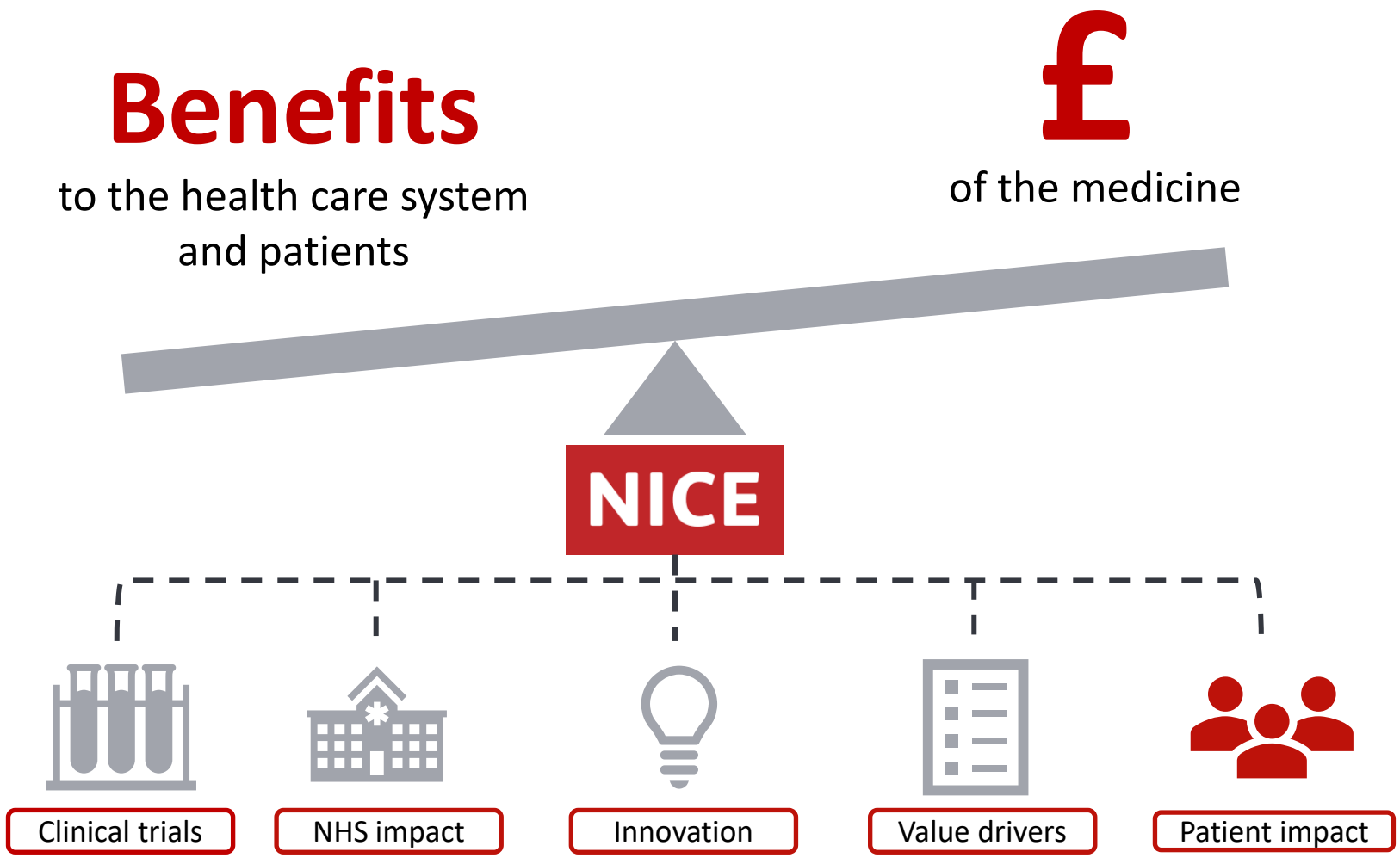
HIV

Rheumatoid Arthritis

Hepatitis C

What is the challenge associated with combination treatments?

Despite the known clinical benefits associated with combination treatments including improved patient survival and quality of life, it is often very difficult to demonstrate their value. The value of new treatments is assessed by the National Institute for Health and Care Excellence (NICE) in England.



So how does NICE define value?

NICE define value based on cost-utility/cost-effectiveness analysis

Method	How are benefits measured?	How are results expressed?
Cost-utility analysis	Quality-adjusted life years (QALYs)	Incremental cost effectiveness ratio (ICER)

What are quality-adjusted life-years and why are they important?

NICE and other health technology assessment (HTA) bodies use the quality-adjusted life-year as the measurement of value

Costs

- Drug acquisition
- Drug administration
- Concomitant medications
- Follow-up care (outpatient visits and monitoring)
- Safety
- Subsequent therapies

Quality-adjusted life-years

Outcome measure which combines:

- Length of life
- Patient health-related quality of life (patient reported outcomes)

Where does an ICER fit in with this and how does it impact cost effectiveness?

An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of an intervention, compared to an alternative/comparator. This ICER is then compared to a cost-effectiveness threshold which is used to determine whether or not a treatment is 'cost-effective'

Incremental cost-effectiveness ratio for Drug A (new treatment) vs Drug B (existing treatment)

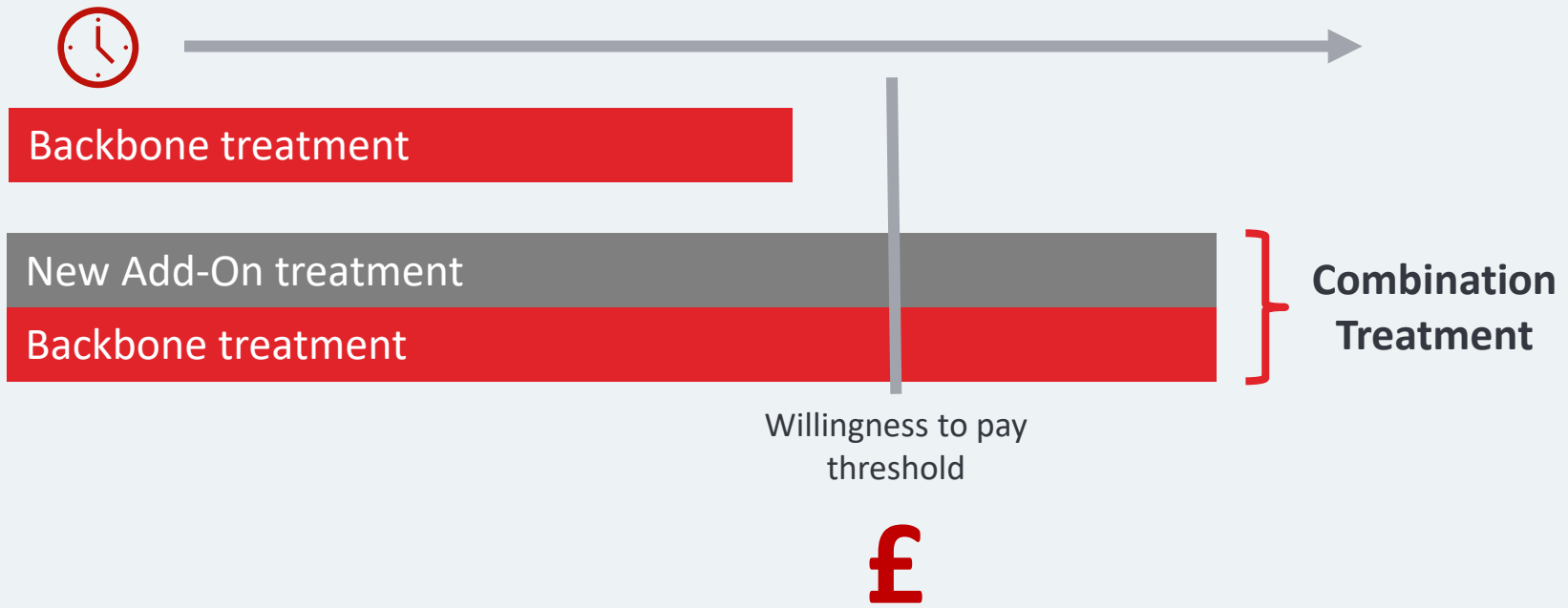
$$ICER = \frac{Costs_{Drug\ A} - Costs_{Drug\ B}}{QALYs_{Drug\ A} - QALYs_{Drug\ B}}$$

Why is it difficult to demonstrate cost effectiveness with combination treatments?

Combination treatments can potentially extend the lives of patients, and these treatments are often used until the patient stops responding. As a result, the backbone treatment is often used for longer as a part of the new combination because the patient is living longer. This alone can increase the cost of the combination treatment to the healthcare system, even before the cost of the add-on treatment is considered.

Adding a novel drug to an already expensive drug or drug combination increases drug acquisition costs significantly. Since all therapies are evaluated at the same willingness-to-pay (WTP) threshold, the combined costs of two or more patented therapies (combination treatments) will often exceed the WTP for a given health benefit.

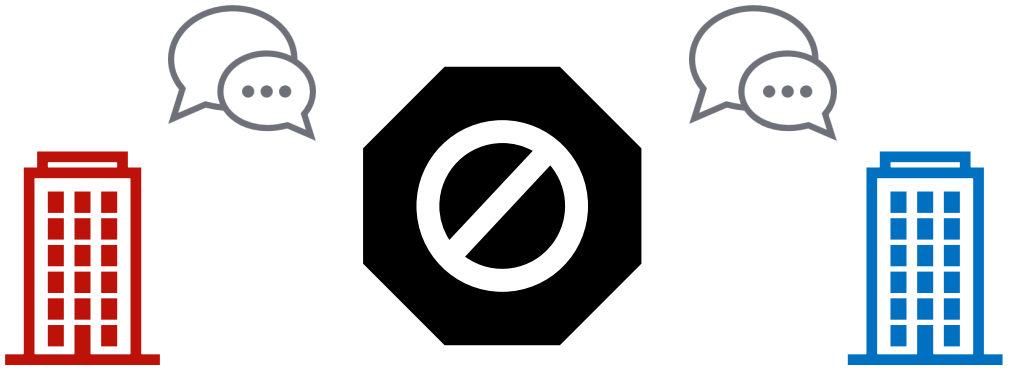
This can sometimes result in the combination not being deemed as cost effective even if the new novel add on was given away for free.



Can we not just change the price of the backbone treatment?

Often treatments included within a combination are developed by different manufacturers, and therefore they are priced independently. In a scenario where a novel add-on therapy is combined with an existing backbone therapy, the manufacturer of the add-on therapy will only have control over the price of its own product and not the overall combination. The existing backbone therapy will already have gone through the appraisal process and have a set price.

This poses a challenge as discussions between companies on commercially sensitive topics such as the cost of treatments are prohibited by strict competition law.



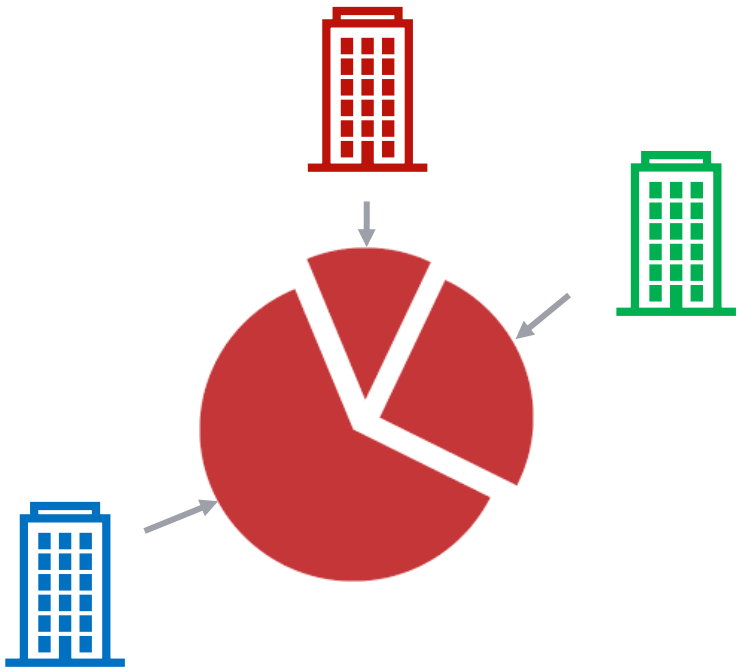
Furthermore, the price of the existing backbone therapy may already be set close to the WTP threshold for its associated health benefits. This leaves little room for the additional cost of the add-on therapy and may prohibit innovation.

So how can we resolve the combination treatments challenge?

Takeda have worked with a number of stakeholders to propose 2 processes that are designed to work together to help improve the complex combination treatments challenge. These 2 processes are centred around:

- A new economic methodology that aims to define a fair division of value across all treatments in a combination, termed as the value attribution framework
- A voluntary arbitration framework that will enable companies to talk in a compliant manner

Value Attribution Framework

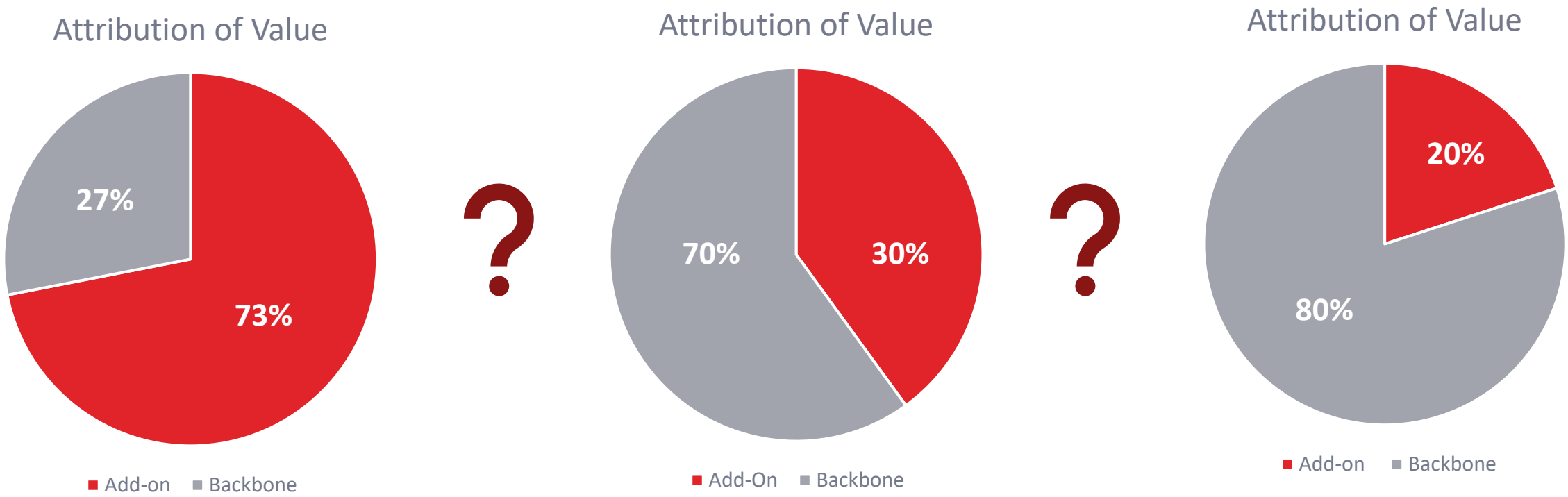


Voluntary Arbitration Framework

The value attribution problem

In order for us to solve the value attribution problem, we first need to understand how much of the benefit of the combination treatment is coming from each individual component medicine.

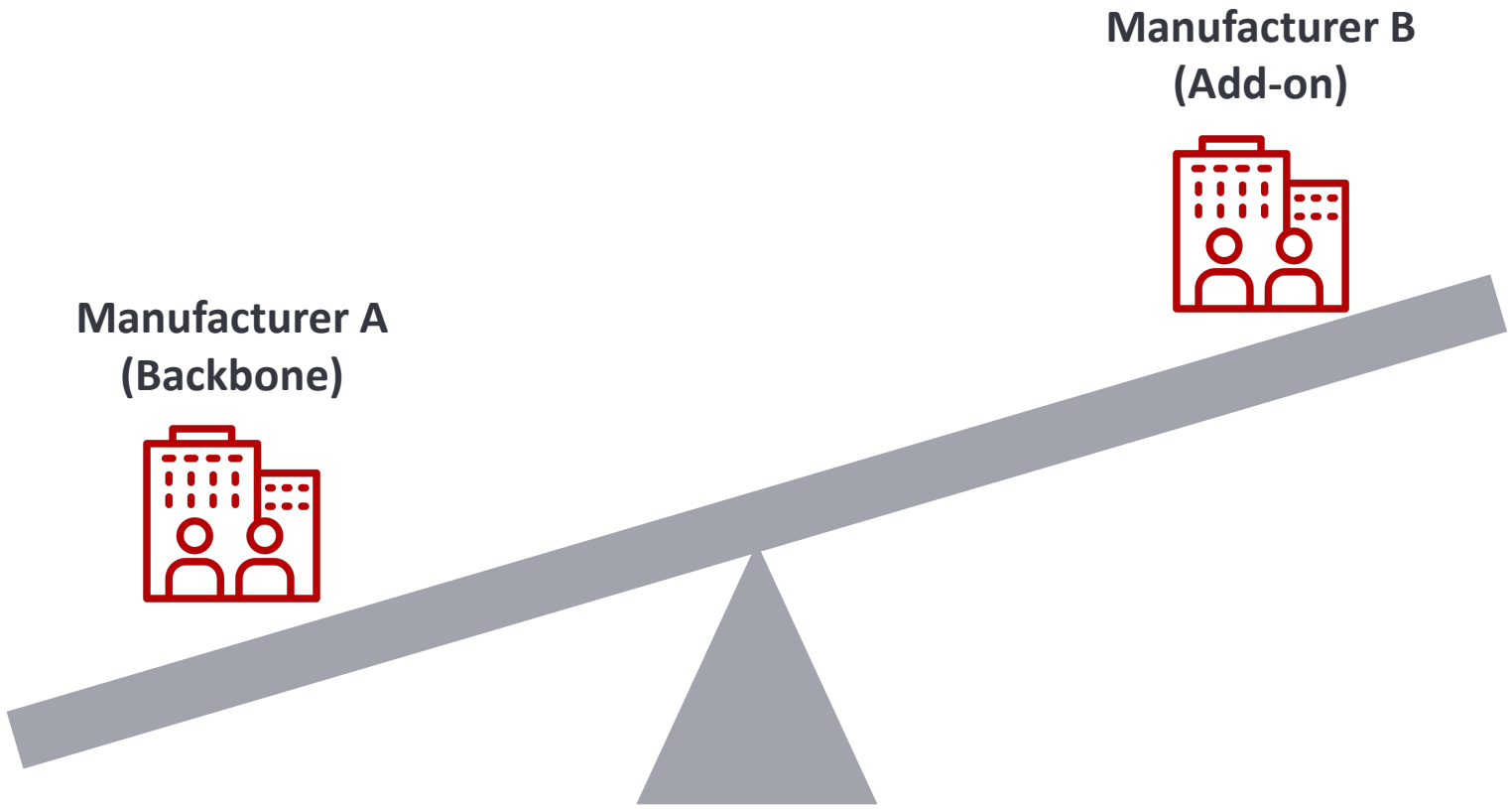
A desirable value attribution strategy would attribute value to each component treatment based on its additional contribution to the health outcome generated by the combination. However, these additional contributions are often difficult to quantify.



How do we determine how much value is coming from each component of the combination treatments?

A desirable value attribution strategy would attribute value to each component therapy based on its marginal contribution to the health outcome generated by the combination. However, these marginal contributions are often difficult to quantify.

Value attribution is also more difficult when component therapies are produced by different manufacturers since this may create potential scenarios where there are perceived “winners” and “losers” (either compared to the status quo or indeed to a perception of what could be achieved).

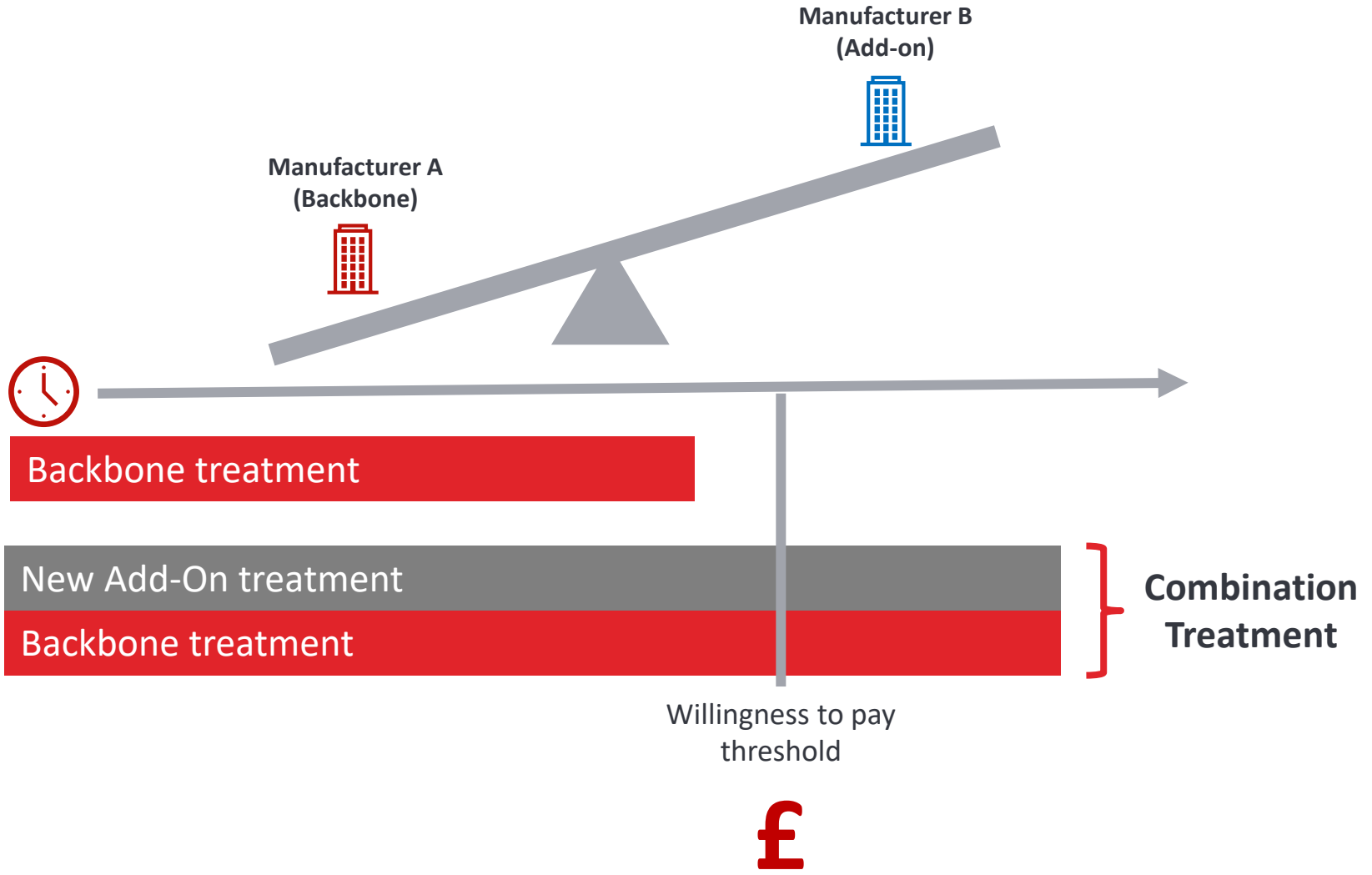


Market Power

A backbone therapy that has already been appraised will be priced near the WTP threshold for the health benefit it generates. There is thus little room for innovation and the additional cost of an add-on therapy if the same WTP threshold is applied to the cost of the combination.

How do we identify when market power exists?

1. Two different companies
2. Backbone already approved and is not required to re-submit
3. Add-on does not have access to the same data from the backbone

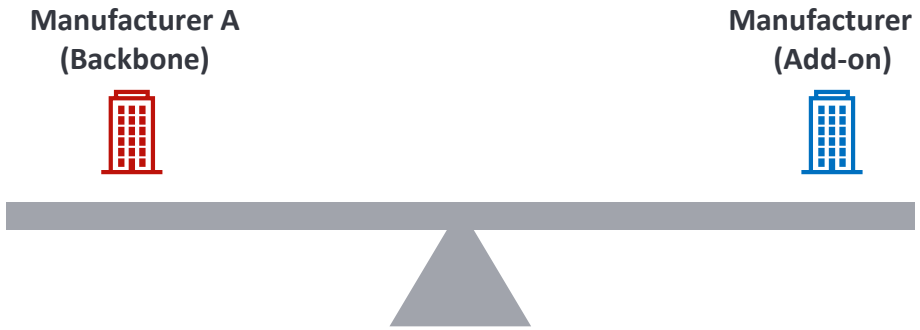


Imbalance of market power

We use the term “imbalanced market power” to define scenarios where the manufacturer of one component therapy has more control over pricing decisions compared to the manufacturer of another component therapy.

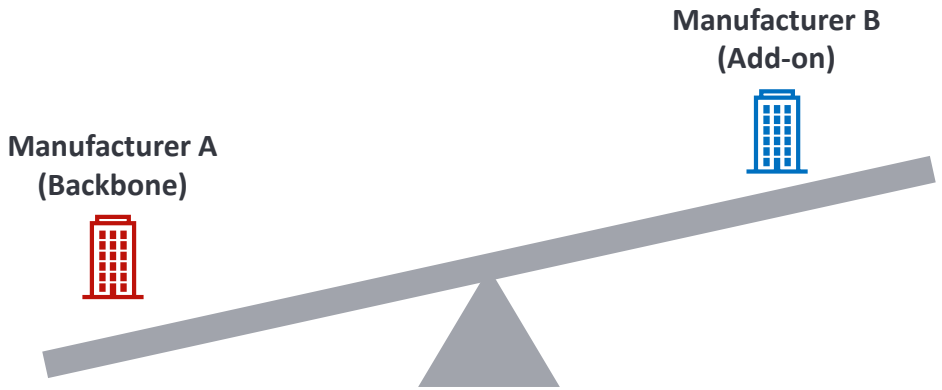
We use the term “balanced market power” to define scenarios where none of the component therapy manufacturers has more control over pricing decisions than another. Market power will often be balanced in cases where a combination treatment consists of two or more existing therapies that have already been appraised and approved and there is no large discrepancy in their respective market shares.

Balanced market power



OR

Imbalanced market power

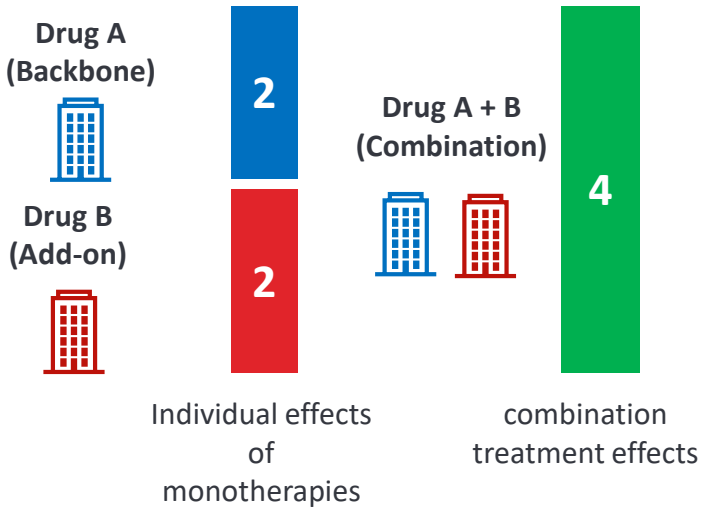


How do we know what value each drug brings to a combination?

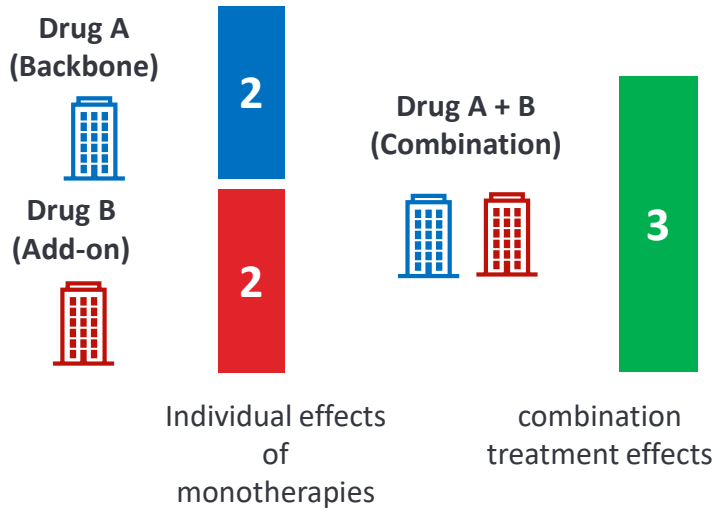
The value of the combination can either be equal to, less than or more than the sum of the values of the individual drugs (monotherapies). With this being the case, we have three terms for each of these scenarios:

1. Additive – The value of the combination is equal to the sum of the monotherapy values for drug A and drug B
2. Sub-additive – The value of the combination is less than the sum of the monotherapy values
3. Synergistic – the value of the combination is more than the sum of the monotherapy values

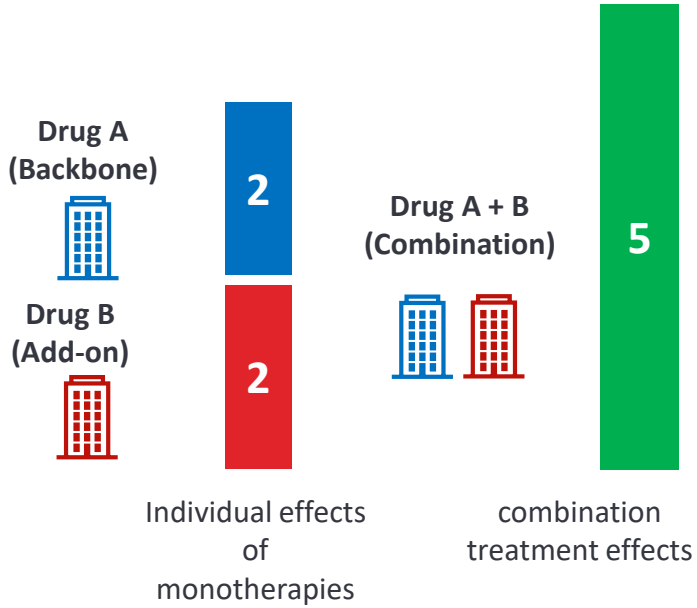
1. Additive



2. Sub-additive



3. Synergistic



The equations

1. Additive – The value of the combination is equal to the sum of the monotherapy values for drug A and drug B

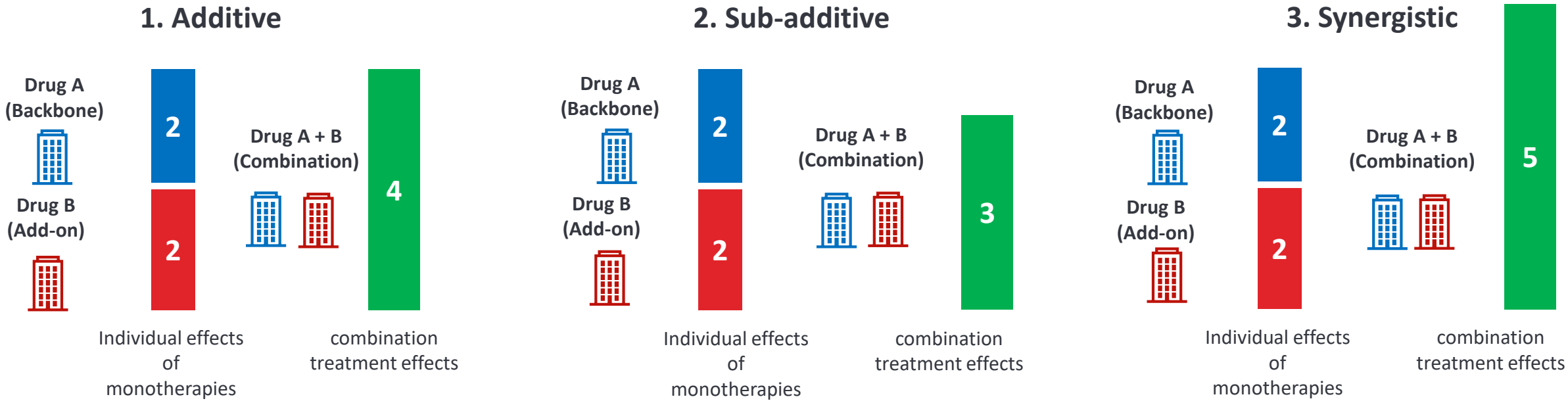
$$Q_{AB} = Q_A + Q_B$$

2. Sub-additive – The value of the combination is less than the sum of the monotherapy values

$$\max(Q_A, Q_B) < Q_{AB} < Q_A + Q_B$$

3. Synergistic – the value of the combination is more than the sum of the monotherapy values

$$Q_{AB} > Q_A + Q_B$$



Q_A= Net-equivalent QALY attained from monotherapy A

Q_B= Net-equivalent QALY attained from monotherapy B

Q_{AB}= Net-equivalent QALY attained from combination treatment of A and B

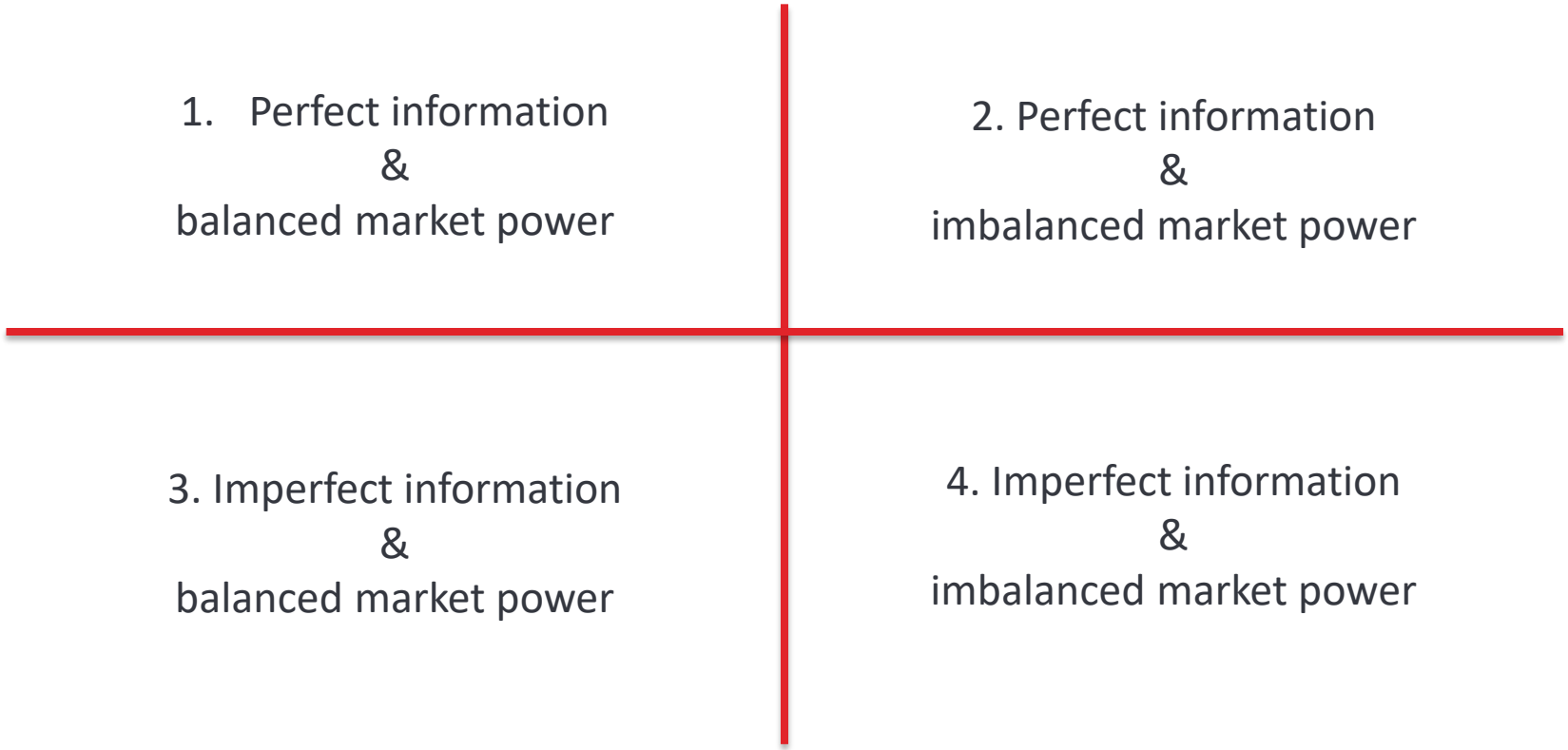
Perfect and Imperfect information

Perfect information: There is data or clinical studies on each treatment independently and as a combination together

Imperfect information: There is data or clinical studies on the combination together and on the backbone treatment; however, there is no data on the add-on treatment alone

How many potential scenarios are there when assigning value?

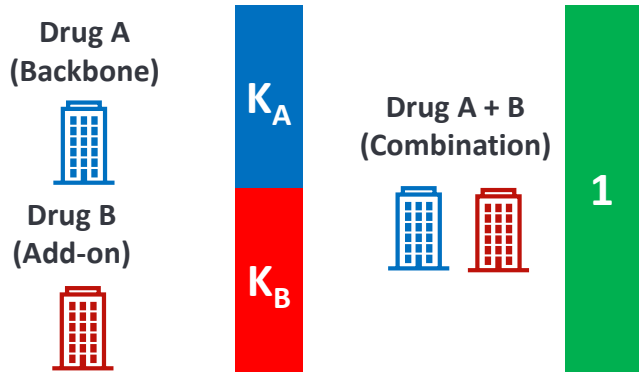
We consider there to be four potential scenarios when assigning value:



The Value Attribution Framework

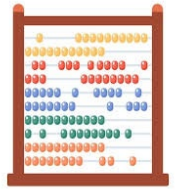
For us to create a solution, we must create a framework that enables us to allocate value to each proportion of the combination therapy.

Consider the combination treatment with component therapies A and B. Let k_A be the proportion of the value of the combination treatment that is attributed to Therapy A, and let k_B be the proportion of the value that is attributed to Therapy B, where $k_A + k_B = 1$.



We present a framework for selecting values for k_A and k_B that accounts for differences in the clinical effectiveness of therapies A and B as well as the balance of market power

How do you assign value for Perfect Information and Balanced Market Power?



= Effect of drug A

= Effect of drug B

Perfect Information and Balanced Market Power

Monotherapy Effects

Drug A (Backbone) — Monotherapy

Drug B (Add-on) — Monotherapy

Sum of monotherapy effects as a combination

Additive

Sub-Additive

Synergistic

Assigned Value

Where the combination is additive the value is assigned evenly based on the effects of the individual monotherapies

Where the combination is sub-additive, both manufacturers share a reduction in value

When the combination is synergistic, both manufacturers share the increase in value

Additive – The value of the combination is equal to the sum of the monotherapy values for drug A and drug B
Sub-additive – The value of the combination is less than the sum of the monotherapy values
Synergistic – the value of the combination is more than the sum of the monotherapy values

How do you assign value for Perfect Information and Balanced Market Power?

Perfect Information and Balanced Market Power

$$k_A = \frac{Q_A}{Q_A+Q_B} \text{ and } k_B = \frac{Q_B}{Q_A+Q_B}$$

Monotherapy Net-equivalent QALY

Q_A Q_B

Drug A (Backbone) — **Monotherapy**

Drug B (Add-on) — **Monotherapy**

Combination net equivalent QALY

Additive

$Q_{AB} = Q_A + Q_B$

Sub-Additive

$\max(Q_A,Q_B) < Q_{AB} < Q_A + Q_B$

Synergistic

$Q_{AB} > Q_A + Q_B$

Assigned Value

$k_A = \frac{Q_A}{Q_A+Q_B}$ $k_B = \frac{Q_B}{Q_A+Q_B}$

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Q_A= Net-equivalent QALY attained from monotherapy A
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K_A= proportion of the value of the combination treatment that is attributed to Therapy A
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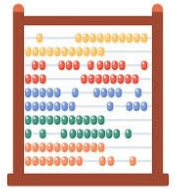
How do you assign value for perfect information and imbalanced market power?



= Effect of drug A

= Effect of drug B

Perfect Information and Imbalanced Market Power

Monotherapy Effects

Drug A (Backbone)

Monotherapy

Has more market power as it is the original backbone

Drug B (Add-on)

Monotherapy

Sum of monotherapy effects as a combination

Additive

Sub-Additive

Synergistic

Assigned Value

Where the combination is additive the value is assigned evenly based on the effects of the individual monotherapies

Manufacturer A is assumed to keep the value attribution already assigned and only allow manufacturer B to gain the additional value up to the total value of the combination

It is more favourable for manufacturer A to adopt the solution that shares the value of the combination products in proportion to their monotherapy effects

Additive – The value of the combination is equal to the sum of the monotherapy values for drug A and drug B
Sub-additive – The value of the combination is less than the sum of the monotherapy values
Synergistic – the value of the combination is more than the sum of the monotherapy values

How do you assign value for perfect information and imbalanced market power?

Perfect Information and Imbalanced Market Power

$$k_A = max\left(\frac{Q_A}{Q_{A,B}}, \frac{Q_A}{Q_A+Q_B}\right) \text{ and } k_B = min\left(\frac{Q_{A,B}-Q_A}{Q_{A,B}}, \frac{Q_B}{Q_A+Q_B}\right)$$

Monotherapy Net-equivalent QALY

Q_A Q_B

Drug A (Backbone)

Monotherapy

Has more market power as it is the original backbone

Drug B (Add-on)

Monotherapy

Sum of monotherapy effects as a combination

Additive

Sub-Additive

Since the manufacturer of Therapy A has the "first-mover advantage", it has less incentive to accept a share of the value of the combination that is less than the monotherapy value of Therapy A.

Synergistic

Assigned Value

Where the combination is additive the value is assigned evenly based on the effects of the individual monotherapies

$$k_A = max\left(\frac{Q_A}{Q_{A,B}}, \frac{Q_A}{Q_A+Q_B}\right) \quad k_B = min\left(\frac{Q_{A,B}-Q_A}{Q_{A,B}}, \frac{Q_B}{Q_A+Q_B}\right)$$

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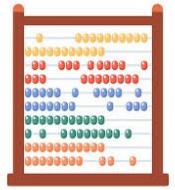

= Effect of drug A

= Effect of drug B

Imperfect Information and Balanced Market Power

Monotherapy Effects

Drug A (Backbone)

Monotherapy

Drug B (Add-on)

Monotherapy

There is imperfect information as drug B has only been studied in combination with drug A and therefore there is no monotherapy data

Sum of monotherapy effects as a combination

There is no way to know if the combination (Drug A + Drug B) represents additive, sub-additive, or synergistic effects. This is due to the monotherapy effects of treatment B not being known

Assigned Value

In this scenario we would assume a solution balanced between manufactures and assume additive effects of the components.

This would suggest that the backbone treatment retains its monotherapy value. The add-on treatment receives the incremental value between the value of the combination treatment and treatment A.

Additive – The value of the combination is equal to the sum of the monotherapy values for drug A and drug B
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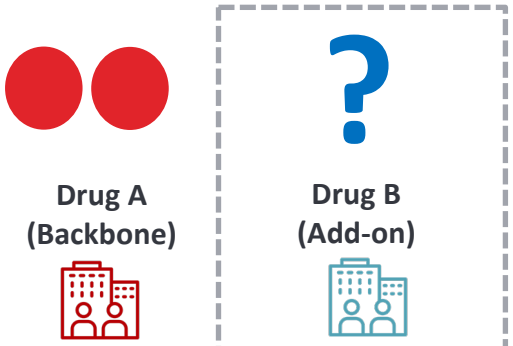
Imperfect Information and Balanced Market Power

$$k_A = \frac{Q_A}{Q_{A,B}} \text{ and } k_B = \frac{Q_B}{Q_{A,B}} = \frac{Q_{A,B} - Q_A}{Q_{A,B}}$$

Monotherapy Effects



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Assigned value of therapy A

$$k_A = \frac{Q_A}{Q_{A,B}}$$

Assigned value of therapy B

$$k_B = \frac{Q_B}{Q_{A,B}} = \frac{Q_{A,B} - Q_A}{Q_{A,B}}$$

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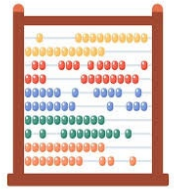

= Effect of drug A

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Imperfect Information and Imbalanced Market Power

Monotherapy Effects

Drug A (Backbone) — **Monotherapy**

Drug B (Add-on) — **Monotherapy**

Company A has more market power as it owns the original backbone therapy. There is imperfect information as drug B has only been studied in combination with drug A and therefore there is no monotherapy data

Sum of monotherapy effects as a combination

There is no way to know if the combination (Drug A + Drug B) represents additive, sub-additive, or synergistic effects. This is due to the monotherapy effects of treatment B not being known

Assigned Value

Manufacturer A can be expected to exert its market power such that the incremental benefit of the combination may not all be attributed to the add-on treatment (as in the balanced market power case). In the imbalanced case, the range of a negotiated share of the incremental benefit is theoretically large, from 0-100% of that incremental benefit.

A pragmatic solution is to consider that this attribution should stand where the add-on treatment is assigned less than 50% of the combined value under the balanced power solution.

Where the add-on treatment would be assigned more than 50%, then manufacturer A should be assigned a proportion of the incremental benefit of the combined value to equalise the value share.

Additive – The value of the combination is equal to the sum of the monotherapy values for drug A and drug B
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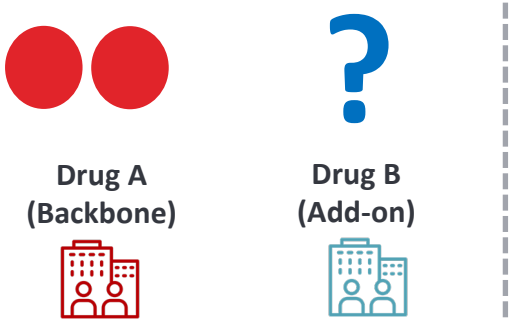
How do you assign value when there is imperfect information and imbalanced market power?

Imperfect Information and Imbalanced Market Power

$$\frac{Q_A}{Q_{A,B}} \leq k_A < 1 \text{ and } 0 < k_B \leq \frac{Q_{A,B}-Q_A}{Q_{A,B}}, \text{ with } k_A + k_B = 1.$$

Monotherapy Effects



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A pragmatic solution is to consider that this attribution should stand where the add-on treatment is assigned less than 50% of the combined value under the balanced power solution.

Where the add-on treatment would be assigned more than 50%, then manufacturer A should be assigned a proportion of the incremental benefit of the combined value to equalise the value share.

$$\begin{cases} \frac{Q_A}{Q_{A,B}} \leq k_A \leq (1+p) \cdot \frac{Q_A}{Q_{A,B}}, & \text{if } \frac{Q_A}{Q_{A,B}} < 0.50 \\ k_A = \frac{Q_A}{Q_{A,B}}, & \text{if } \frac{Q_A}{Q_{A,B}} \geq 0.50 \end{cases}$$

Q_A= Net-equivalent QALY attained from monotherapy A
Q_B= Net-equivalent QALY attained from monotherapy B
Q_{AB}= Net-equivalent QALY attained from combination treatment of A and B
K_A= proportion of the value of the combination treatment that is attributed to Therapy A
K_B= proportion of the value of the combination treatment that is attributed to Therapy B

Thank you

Better Health, Brighter Future