Challenges in valuing and paying for combination regimens in oncology

Report of an international workshop convened by Bellberry, held on November 18-20, in Sydney, Australia

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May 2020

Contents

1. Executive Summary

In November 2019 Bellberry convened a three day international workshop, inviting experts representing all relevant stakeholders from around the world to discuss the challenges associated with valuing and paying for combination regimens in oncology. Cancers arise through aberrations in multiple biological pathways, meaning that treatments that target only one of these pathways may not provide long lasting benefit to patients. Therefore, it is common to treat cancers with multiple drug treatments, called combination therapies. Combination therapies are often expensive, especially when multiple on-patent treatments are combined, which makes paying for them challenging for health systems around the world. This is particularly the case when different companies own the on-patent treatments that are combined, because this may inhibit flexibility in pricing. Hence, this report primarily considers the case where combination therapies consist of two or more on-patent treatments, owned by two or more companies.

Health Technology Assessment (HTA) is used to determine which treatments health systems should pay for, at what price. Different systems work in different ways and have different constraints and decision-making processes. However, fundamentally, treatments must be seen to represent good value for money in order to be paid for. Given this, therapies are usually priced at a level which health systems are willing to pay, given the value (e.g. clinical benefit) the therapy provides.

Combination therapies are usually developed in one of two ways: two or more existing therapies might be combined, or one new therapy might be added to existing therapy. The problems that this brings for valuation and payment can be demonstrated with two simple hypothetical scenarios.

First, consider two drugs that already exist as monotherapies. Imagine that both bring a value of ‘1’, and are correspondingly priced at ‘1’. Combining the two drugs provides a value of 1.5, but at a price of 2. The combination therapy provides more value (i.e. clinical benefit) than either of the drugs provided alone, but whilst the price of therapy has doubled, the value has not. Hence, the combination would not be considered good value for money.

Second, consider a case where one drug exists as a monotherapy, and an add-on therapy is developed. The existing monotherapy must be given in every additional month lived, and is priced so that providing each extra month of life is just considered to be good value for money. When combined with the existing therapy, the new add-on therapy results in patients living an extra 12 months, but also results in 12 months more treatment with the existing therapy. Because the existing therapy is already priced to the level that each additional month of survival is only just considered good value for money, there is no headroom left for any additional costs associated with the new add-on therapy. Hence, the combination would not be considered good value for money – in some circumstances, even if the add-on therapy was provided at zero price.

From a societal perspective and from an ethical perspective this is problematic because in both cases the combination therapy has value to patients and society, but is unlikely to be purchased because it does not represent good value for money.

During the Bellberry workshop three potential solutions to this issue were discussed:

1. **Increase the value of the combination therapy through improved clinical development and design.** Through optimising treatment regimens toxicity could be reduced, quality of life could be improved, and costs could be reduced, thereby increasing the value of combination therapies and making it more likely that these would represent good value for money. There was wide support for the notion that clinical development and the design of clinical trials for combination therapies was sub-optimal. More thought should be given to the design of clinical trials, including the type of treatment regimens, stopping rules, measures of outcome relevant to patients, and comparators. Better use should be made of post-launch studies and real world data. Combined scientific advice from all relevant stakeholders can help enable this.
2. **Alter HTA processes, increasing the willingness to pay specifically for combination therapies.** The challenges associated with paying for combination therapies would be removed to some extent if HTA agencies/payers were willing to pay more for them. However, there was wide agreement amongst meeting attendees that there is not currently a case for altering HTA decision rules or deliberative frameworks specifically for combination therapies. For instance, if a monotherapy and a combination therapy provided the same benefit, meeting attendees did not see why health systems should be willing to pay more for the combination therapy.
3. **Negotiate prices with flexible payment and pricing mechanisms.** There was wide support for the notion that the price of existing therapies should be re-visited, with respect to their use within combinations, when add-on therapies are combined with them to provide proven clinical benefit. Similarly pricing should be reconsidered when existing monotherapies are combined. The aim should be to ensure that the price of the combination therapy is commensurate with its value, whilst also allowing prices for constituent parts that are acceptable to their manufacturer. Practically, this requires HTA agencies and payers to communicate clearly with manufacturers to determine what type of flexible pricing model is acceptable to achieve price adjustments for use in combination therapy in their jurisdiction. A form of multi-use pricing is likely to be required and health systems are likely to need to have in place appropriate data collection systems to facilitate this – though expected utilisation models may be considered sufficient. Decisions would also need to be made as to who (manufacturer, HTA agency, payer) should be responsible for attributing value (and prices) to the constituent parts of a combination therapy, and how this should be done. Meeting attendees felt that more research is needed on value attribution approaches and that there is an urgent need for manufacturers, payers and HTA agencies to explore the legalities of price negotiations between companies (possibly with the involvement of HTA agencies and payers) in different jurisdictions around the world. Meeting attendees also recognised that it is important for all stakeholders to consider how to incentivise companies (particularly manufacturers of backbone therapies) to participate in price negotiation.

Improved clinical development and design and flexible pricing and payment mechanisms represent the two key options for helping ensure appropriate patient access to clinically effective combination therapies in cancer. There is an urgent need for pharmaceutical companies, HTA agencies and payers to further explore the legal challenges associated with price negotiation between companies, with the aim of ensuring that negotiations may be pursued in all jurisdictions around the world. Furthermore, flexible pricing needs to be implementable within health systems. In addition, mechanisms for attributing value between constituent parts of combination therapies are needed. In tandem, it is crucial for all stakeholders to encourage open dialogue and joint working for improved trial design to provide evidence on optimal treatment regimens that increase benefits to patients and reduce costs to health systems.

2. Introduction

In November 2019 Bellberry convened an international workshop, inviting experts from around the world to discuss the challenges associated with valuing and paying for combination regimens in oncology. The primary focus of the workshop was on the situation where combination therapies consist of two or more on-patent treatments, owned by two or more companies. Attendees at the workshop included clinicians, patient representatives, health technology assessment (HTA) agency staff and experts, pharmaceutical company staff, academics, health economists, ethicists, regulatory agency representatives, health care payers and lawyers (see Annex 1 for a list of attendees). Nick Latimer and Dan Pollard from the University of Sheffield performed the duties of the Scientific Secretariat for the workshop, assisted by Adrian Towse and Chris Henshall. Chris Henshall facilitated the workshop.

Prior to the workshop attendees were sent pre-read documents, including relevant published papers and reports and a core paper written by the Scientific Secretariat to facilitate discussion at the workshop. The structure of the workshop followed that of the core pre-read paper and spanned three days. The workshop was split into two sections; Days 1 and 2 were attended by invited stakeholders only, whereas Day 3 was a public meeting.

On Day 1, attendees were informed by leading oncologists of the clinical factors driving the increasing development and use of combination therapies in cancer. Attendees were then presented with the challenges to health care systems that arise when it comes to valuing and paying for combination therapies. Next, meeting attendees from different HTA agencies and countries were asked to give short presentations explaining what issues combination regimens in oncology had raised in their country, and how their system had responded. Following this, a selection of meeting attendees with different perspectives presented their view of the situation, outlining what they saw as the key issues. After this, focus switched to discussion of potential options for addressing the challenges that had been identified in the previous sessions. First, attendees were presented with an overview of options identified from the literature, and were updated on relevant work being done by HTA agencies and pharmaceutical companies. Attendees were then asked to split into breakout groups to consider the options and in particular were asked to consider which options they felt could realistically be developed and implemented to address the challenges presented by combination regimens.

On Day 2 of the workshop the breakout groups reported back on their thoughts and a possible structure for a meeting report, and key messages to be included in it, were discussed in a plenary session. Breakout groups were then asked to consider the proposed content of the meeting report and subsequently reported back on this. Finally, a panel of stakeholders with different perspectives gave their views on the previous two days of discussion.

Day 3 consisted of a public meeting, where the Scientific Secretariat presented a summary of the workshop to a wider audience. Again a panel of stakeholders presented their views, followed by a facilitated discussion during which, in particular, attendees were asked to highlight any additional points not covered during Days 1 and 2 of the workshop.

This report represents the Scientific Secretariat's interpretation of the discussion heard during the three days of the Bellberry workshop. It does not attempt to make any consensus statements, but, where relevant, we indicate levels of support for a variety of views and statements. The remainder of this report has 6 sections. In Section 3, we provide background on combination therapies in cancer and implications for pricing and reimbursement systems, and define terms. In Section 4 we describe the challenges associated with valuing and paying for these therapies. In Section 5 we consider how these challenges manifest in different health systems. In Section 6 we describe options to address the challenges identified. In Sections 4-6 we draw on discussion heard during Days 1 and 2 of the workshop. In Section 7 we highlight additional issues identified on Day 3 of the workshop that were not discussed on Days 1 or 2. Finally, in Section 8, we summarise potential action points and draw conclusions.

3. Background

Single agent therapies alone may not provide long-lasting benefit for many cancer patients.[1] Cancers often arise through the accumulation of several genetic events or genomic alterations and consequent alterations in many molecular pathways. These aberrant cells are not detected and removed by the immune system. Therefore, it is often the case that a single agent is unable to prevent cancer growth significantly and durably.[1,2] For this reason it has long been common for combination treatments to be used to treat many cancers. More recently it has become increasingly common for two or more *on-patent* treatments to be combined and it is this that results in pricing and payment challenges – particularly when different companies own the on-patent treatments being combined.

We refer to the components of a combination regimen as 'constituent therapies'. The 'backbone therapy' is the therapy registered first, and 'add-on therapies' are therapies that are later registered as treatments to be given in combination with backbone therapy. This follows the terminology used by Danko *et al.*[2] Over time, as combination therapies become standard practice, the combination therapies themselves may become backbone therapies, and new add-on therapies may be combined with these.

As more therapies are developed and added to backbone therapy (or therapies), market access problems may arise. In particular, costs are likely to rise, as the price of providing the add-on therapy is added to the cost of providing the backbone therapy. Usually, health technology assessment (HTA) agencies and pricing and reimbursement bodies assess combination treatments as one overall treatment package, and consider whether the value of that package is sufficient to grant it reimbursement.

When a single agent is being assessed, payers in many systems will assess the value of the new treatment and decide whether that value is sufficient to permit reimbursement, given the price being charged for the treatment. Henceforth, we refer to systems taking this approach as "price taking" systems. Alternatively, some payers will determine the price at which they are willing to permit reimbursement, based upon the payer's assessment of the value that the new treatment provides. Henceforth, we refer to these systems as "price setting" systems.

In a price taking system, the provider of the treatment has control over the price of the treatment and, if required, has the power to alter the price in order to achieve reimbursement. However, when a combination treatment is being assessed the company who developed the add-on therapy may have relatively little control over the price of the overall treatment package, if the backbone therapy is provided by a different company. Without negotiation between the providers of the constituent therapies the cost of the backbone therapy may be considered as fixed, leaving the producer of the add-on therapy with the power only to amend the price of a portion of the overall combination.

The problem is similar in price setting systems, with the payer or HTA agency seemingly likely to focus on the price at which they are willing to reimburse the producers of the new treatment. However, theoretically, the agency could also re-set the price that they are willing to pay for the backbone therapy without the need for discussions between manufacturers.

In either system, this may make it difficult for producers of add-on therapies and payers to agree on a price that results in the payer being satisfied with the value of the combination, and which also provides the producer with a return that they deem acceptable. Indeed, it has been observed that in health systems that use cost-effectiveness assessment, add-on therapies are often found to be not cost-effective – sometimes even when the add-on therapy is allocated a zero price.[3]

From a societal health perspective and from an ethical perspective this is problematic, because as long as a new combination therapy provides clinical benefit compared to existing therapy, there exists a price at which the combination is considered good value for money. But, if the producer of the backbone therapy is unable or unwilling to change the price, or if a price setting payer does not re-set the price that they are willing to pay for the backbone therapy, the producer of the add-on therapy may not be able to set (or agree to) a price that results in the price of the combination being acceptable to the payer whilst providing an adequate return to the producer. It is important to re-iterate that this problem only usually arises when the backbone therapy involves one or more on-patent treatments and therefore has a relatively high price. Combinations that only involve off-patent treatments, or only one on-patent treatment, are likely to avoid the challenges discussed in this report.

4. Challenges

The challenges associated with valuing and paying for combination therapies in cancer can be illustrated simply using two hypothetical scenarios. In reality, situations are usually much more complex, but these scenarios explain the fundamental problems that arise when combination therapies are developed.

First, consider a case where two drugs already exist as monotherapies, and each is priced at a level that is justified based on the value that it brings. Imagine that both bring a value equivalent to '1' (in whatever units are considered relevant in the system in question), and are correspondingly priced at '1'. Then it is discovered that combining the two drugs provides a value of 1.5, but at a price of 2. The combination therapy provides more value (i.e. clinical benefit) than either of the drugs provided alone, but whilst the price of therapy has doubled, the value has not. Hence the combination therapy may not be considered good value for money.

Second, consider a case where one drug exists as a monotherapy, and an add-on therapy is developed. The existing monotherapy (the backbone) must be given in every additional month lived, and is priced so that providing each extra month of life is just about considered to be good value for money. When combined with the backbone therapy, the new add-on therapy results in patients living an extra 12 months, which means the patient receives 12 months more treatment with the backbone therapy. Because the backbone therapy is already priced to the level that each additional month of survival is only just considered good value for money, there is no headroom left for any additional costs associated with the new add-on therapy. Despite contributing to an additional 12 months of survival, the add-on therapy would only be considered good value for money if it cost nothing – because all of the allowable costs are already taken up by the additional 12 months of treatment with the backbone therapy.

It is important to recognise that these issues only usually arise when two or more on-patent drugs are combined. For example, scenario 1 arises when two or more drugs are combined that are each already priced to their value – that is, their price represents the maximum that the health system is willing to pay for them, given the value that they bring as monotherapies. If one of the drugs was off-patent and priced at 0.1 (because of the effects of competition) then the combination would bring a value of 1.5 at a price of 1.1 and would be considered good value for money. Similarly, scenario 2 arises when a new add-on therapy is added to an on-patent drug that is priced to the maximum that the health system is willing to pay for it. If the add-on therapy was added to an off-patent drug there would likely be considerable headroom for a reasonable price to be charged for the add-on therapy.

Nevertheless, it is not uncommon for two or more on-patent drugs to be combined, and the scenarios described above have arisen in practice. For example, in 2013 the United Kingdom's National Institute for Health and Care Excellence (NICE) appraised pertuzumab in combination with trastuzumab and docetaxel for adults with Human epidermal growth factor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.[4,5] Trastuzumab and docetaxel

represented the backbone therapy, and pertuzumab represented the add-on therapy. Notably pertuzumab has no activity as a monotherapy.

The NICE Appraisal Committee concluded that the combination treatment provided a progression-free survival (PFS) gain of approximately 6 months compared to the backbone therapy alone, but that there was uncertainty around the difference in overall survival due to the immaturity of the data from the clinical trial.[4,5] Similar conclusions were drawn by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.[6] Under the assumption that there was no post-progression survival difference between the backbone therapy and the combination therapy, the 6 month PFS gain would lead to a 6 month overall survival gain, but would come at the cost of an extra 6 months of treatment (because treatment was indicated to continue until disease progression). According to calculations made by NICE's Decision Support Unit (DSU), the cost of remaining in PFS for 6 months was £13,627, even if pertuzumab had zero price – this cost was made up of the drug costs for trastuzumab and docetaxel, the costs of administering these drugs and pertuzumab, pharmacy dispensing costs and supportive care costs.[3]

NICE typically considers new treatments to be cost-effective if they provide one additional quality adjusted life year (QALY) for an incremental cost of less than £20,000 to £30,000. QALYs take into account length of life and quality of life, and the quality of life (utility) score associated with PFS used in the pertuzumab appraisal was 0.785 (where perfect health would achieve a score of 1.00 and death would achieve a score of 0.00). Hence, 6 additional months of PFS were worth 0.5*0.785 = 0.393 QALYs. Therefore, the incremental cost per QALY gained for the combination therapy, based on the 6 month PFS gain, would be £13,627/0.393 = £34,712, even if pertuzumab had zero price. Hence, because of the high cost of backbone therapy, add-on therapy with pertuzumab would not be considered cost-effective even if it had zero price.

This demonstrates that if backbone therapy is priced to the maximum that the health system is willing to pay for it (or indeed is priced at an even higher level), then, by definition, any therapy that is added to this will not be considered cost-effective, even if it delivers clinical benefit, if the backbone therapy is also required to be given in any additional month lived.

5. Do the issues raised by combination therapies differ according to the approaches taken to assess value and determine reimbursement in different systems?

HTA agencies adopt one of two basic approaches to assessing the value of treatments: a "therapeutic added value" approach where outcomes are expressed in clinical terms (as is the case in France and Germany, for example); or an approach where clinical outcomes are weighted using utilities to estimate Quality Adjusted Life Years (QALYs), as in the UK, Sweden, Canada and Australia (often referred to as a "QALY" approach).

When HTA agencies and payers appraise combination therapies, the core issues that must be addressed are:

1) Do the outcomes expected from the combination of drugs justify the overall cost of the treatment (or, what overall cost would be appropriate for the outcome expected)? and if not,

2) Can an acceptable price or prices be negotiated for the drugs involved in light of the expected clinical outcomes.

This approach is, in principle, the same regardless of whether the payer adopts a therapeutic added value or a QALY approach. Whichever approach is used, the situation can arise where the combination therapy – comprising of the backbone therapy and the add-on therapy – is more effective than the backbone therapy alone, but a price cannot be agreed upon that is satisfactory to both the producer of the add-on therapy and the payer or HTA agency. In extreme cases, it may be the case that no positive price exists for the add-on therapy that would be considered to represent good value for money. Whilst issues such as "not cost-effective at zero price" become most apparent in systems that explicitly estimate cost-effectiveness, issues associated with access to combination treatments have also been reported to exist in countries where HTA focuses on added clinical benefit.[2] This is not surprising since the overall price of a combination will be expected to be commensurate with its overall value in any system involving value assessment, and if the price of the backbone therapy is already fixed and relatively high, there will be little margin for agreeing an appropriate price for the add-on therapy or adjusting the price of the backbone therapy.

Whilst healthcare valuation, payment and reimbursement mechanisms around the world differ in many ways, the same fundamental problems remain with respect to combination therapies for cancer. These issues apply regardless of whether the payer operates a price taking or price setting system, since in both cases the agreed price must be acceptable to both the producer of the add-on therapy and the payer or HTA agency. At the Bellberry workshop, there was representation from systems using therapeutic added value as well as those using QALYs and, while much of the discussion focussed on how the issues manifested themselves and might best be addressed in QALY-based systems, there was strong support for the notion that, while the details may vary between different systems, combination therapies in cancer present important challenges for most valuation and payment mechanisms, both in terms of affordability and value for money.

6. Options to address the issues associated with valuing and paying for combination therapies in cancer

Discussion at the workshop was informed by pre-read documents, including a review which aimed to identify issues associated with valuing and paying for combination regimens in oncology that have been identified and discussed in the literature.[7] The review paid particular attention to options for addressing these issues that have been suggested in the literature. In addition to this, meeting attendees were asked prior to the meeting what they viewed as the three key valuation and reimbursement issues and challenges raised by combination regimens, and what they saw as the key solutions/ways forward. Attendees were also asked whether they were engaged in, or aware of, any current work on solutions – theoretical and/or practical – to the challenges raised by combination regimens. Together, these sources of information formed the basis for detailed discussion on how the issues associated with combination therapies could be addressed. In this Section, we present our interpretation of this discussion.

Summary

The general challenge associated with valuing and paying for combination therapies, described in Section 4, is that the price of the combination is often too high, given its perceived value. In this situation, if combination therapies that deliver clinical benefit are to be made available to patients, three possibilities exist:

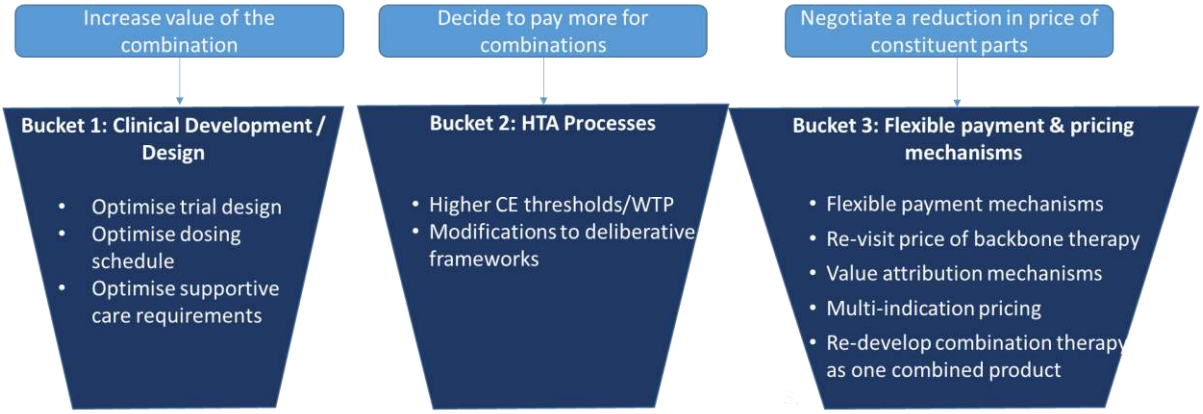
1: Increase the value of the combination. Through improved **clinical development and design** an evidence base for the clinical benefit associated with the combination could be improved, thus increasing the demonstrable value of the combination

2: Be willing to pay more for the combination. **HTA processes** could be amended, such that the willingness to pay for combination therapies is increased

3: Reduce the price of the combination. Through **flexible payment and pricing mechanisms** the price of the constituent parts of the combination could be re-visited and negotiated

Based upon this, options for addressing the challenges associated with valuing and paying for combination therapies in oncology were placed into three 'buckets', focusing on clinical development and design, HTA processes, and flexible payment and pricing mechanisms. Figure 1 summarises these options. We then describe each bucket in more detail, including our interpretation of the views of workshop attendees on these.

Figure 1: Three Buckets – options to address the challenges associated with valuing and paying for combination therapies in cancer



Bucket 1: Clinical Development and Design

Concept

The concept underlying this bucket is that it may be possible to increase the benefits to patients associated with combination therapies without increasing their costs (or perhaps even reducing their costs) through optimising treatment regimens. This idea is relevant for all healthcare interventions, but there was wide agreement that it could have a particularly large impact in the context of combination therapies. This option was not identified in the literature – it was suggested by workshop attendees.

The optimisation of treatment regimens is particularly relevant for combination therapies because toxicity issues are more likely when multiple treatments are being taken. Lower toxicity is likely to reduce costs and increase quality of life – thereby increasing treatment benefit. In addition, it is common for new cancer treatments to be tested using a "treat to progression" regimen. Workshop attendees felt that sometimes this is necessary, given the mechanism of action of the drugs involved, but that this was not always the case – sometimes after treatment success prolonged treatment is unnecessary and a similar treatment benefit could be expected if a treatment stopping rule was implemented. Continued treatment with all constituent parts of a combination therapy in each additional month lived is a key cause of the problems associated with valuing and paying for combination treatments. Therefore, if stopping rules could be implemented for one or more of the constituent parts – without reducing clinical benefit – valuation and payment problems could be substantially alleviated.

However, when treatment to progression regimens are pursued in clinical trials, evidence on effectiveness in the presence of a stopping rule is lacking. When clinical trial evidence is based on treatment until progression, it may be ethically questionable to apply a stopping rule in practice. Even if there was clinical consensus that a stopping rule could be introduced, it may be challenging for HTA agencies and payers to incorporate these into their decision making, when evidence on effectiveness is from clinical trials that did not include stopping rules.

Many workshop attendees seemed to support the notion that outcomes typically collected in oncology trials are problematic. Measures such as progression-free survival were felt to have limited relevance, and commonly used quality of life and performance status measures were considered sub-optimal. Patient relevant outcomes must be collected in order that the true benefits of treatments can be estimated. Again, this concern is not specific to combination therapies, but is particularly relevant given the impact that highly toxic combinations can have on quality of life.

Overall, many attendees felt that current clinical trial design is sub-optimal in the area of oncology. Some of those present with extensive experience of working in regulatory bodies and industry questioned whether there were realistic alternatives to current practices, and it was acknowledged that regulators such as the FDA and EMA are experts in clinical trial design with decades of experience. However, there was a feeling that better use could be made of more innovative trial designs.

How could this be achieved?

There was wide support amongst workshop attendees for more thought to be given to innovative clinical trial design. Adaptive trial designs allow pre-specified review and adaptation, which could include altered dosing regimens, stopping rules or patient selection (to help direct treatment to patients most likely to benefit).[8]. Platform trials (or adaptive platform trials) allow emerging relevant comparators to be added to ongoing trials, and allow irrelevant comparators to be dropped – potentially allowing different treatment regimens that emerge as valid treatment options to be tested against one another.[9-11]

Better designed trials that investigate optimised treatment regimens could result in increased patient benefit from combination therapies – and could substantially reduce their costs. Conducting trials that seek to maximise patient benefit was seen as an ethical requirement. In addition, trials that investigate these regimens could provide the evidence needed by HTA agencies and payers and this could make it more likely that clinically effective combination therapies would be considered good value for money. Some workshop attendees were concerned that the level of evidence required in order for licenses to be awarded by regulators is low, which makes reliable health technology assessment difficult. It was felt that trials are often too short, have the wrong comparators, and do not collect information on important patient-relevant outcomes.

To address trial design issues attendees generally supported the use of combined scientific advice processes – whereby different HTA agencies, payers and regulators would provide joined-up advice to manufacturers on trial design. Attendees strongly agreed that patients or organisations representing them, and all other relevant stakeholders should be included in the scientific advice process.

In addition, there was wide agreement that pharmaceutical companies and HTA agencies/payers should work to make more use of post-launch studies and real world data to provide information on alternative treatment regimens. Given that substantial amounts of data are already collected on cancer (and other) patients, workshop attendees felt that it is an ethical requirement to make the best use possible of these data. Also, further research is required to identify the most patient-relevant outcome measures to be included in clinical trials.

Bucket 2: HTA Processes

Concept

If there is a desire to make clinically effective combination therapies available to patients, but those therapies are not deemed to be good value for money by whatever HTA mechanism is in place, HTA processes could be amended in a way that means we are willing to pay more for combination therapies for cancer. Most HTA agencies have flexible decision-making criteria, such that recommendations are not based solely on whether a new treatment is estimated to be cost-effective according to a rigidly specified threshold. For example, in Sweden different thresholds are used for different disease areas. In the UK, NICE specifies a threshold range rather than one specific number, the threshold is different for end of life treatments and highly specialised technologies, and Appraisal Committees are encouraged to take into account factors beyond the cost-effectiveness estimate.[12] In systems that look at "therapeutic added value", comparisons are typically made between benefits and costs of a new treatment and those of other treatments for the same condition, with no explicit reference to some generalised "willingness to pay", so there is again inherent flexibility to take account of the specific characteristics of a new treatment when making decisions. Given this flexibility, an option to promote wider access to combination therapies in cancer could be to include 'combination therapies' as a modifier in the decision-making process – essentially meaning that the willingness to pay for these treatments is increased. Alternatively, elements could be added to value frameworks to allow more flexibility through deliberative processes specifically for combination therapies. Exploring differentiated willingness to pay for combination therapies, or adopting value assessment frameworks that consider broader value concepts, have been suggested in the literature as possible solutions to the combination therapy challenges by Danko et al.[2]

Workshop attendees generally agreed that there are benefits to having flexible cost-effectiveness thresholds, broader value frameworks and flexible deliberative processes incorporated into HTA processes. It was also noted that statistical and modelling techniques used to estimate the benefits associated with new treatments continue to evolve. However, attendees considered that if special decision-making provisions were to be made for combination therapies for cancer, there should be evidence-based justification for this. For instance, special provisions for combination therapies for cancer might be implemented because it was known that these were valued more highly by society than any other treatments, including monotherapies for cancer – that is, if a monotherapy provided the same benefit as a combination therapy, the combination therapy would be valued more highly. But workshop attendees did not feel there was any evidence that they are.

In addition, it was recognised that if societal preferences did not support increasing the cost-effectiveness threshold for combination therapies, then doing so in systems with fixed health care budgets could result in lost health overall due to associated disinvestment in other more cost-effective treatments. This would lead to important ethical and efficiency concerns.

How could this be achieved?

Workshop attendees did not see a case for altering HTA decision rules or deliberative frameworks specifically for combination therapies because there was no clear rationale for paying more per unit

of benefit for combination therapies compared to other types of therapy. Therefore, there was not support for putting this option into practice.

Bucket 3: Flexible payment and pricing mechanisms

Concept

This option involves the use of price negotiations, re-assessment and flexible payment and pricing mechanisms to reduce the price of combination therapies, thereby making it more likely that these treatments are considered good value for money and therefore made available to patients. Re-visiting the price of the backbone therapy has been suggested as a solution to challenges presented by combination therapies by Danko *et al.* and Persson and Norlin.[2,13] However, as recognised by those authors, this option raises several issues which need to be addressed around implementation approaches, value attribution, and legal challenges.

For negotiations around the prices of constituent parts of combination therapies to be practically useful, it must be possible to implement the negotiated prices in the health system. Implementation challenges arise because often constituent parts of a combination therapy are already available as a monotherapy in the same disease area, or as a monotherapy or part of a combination therapy in other disease areas. Setting different prices for different uses of a treatment is not straightforward. As suggested by Danko *et al.*,[2] a form of multi-indication pricing (or, more accurately, multi-use pricing) is likely to be required – allowing prices to differ for a treatment depending upon the disease area it is being used in, and depending on whether it is being used as a monotherapy or as part of a combination therapy.[14,15] Alternatively, price discounts or budget caps could be used to achieve equivalent price reductions. Workshop attendees noted that these different mechanisms are in use around the world, but different jurisdictions use different approaches. Moreover, the feasibility of implementing different mechanisms varies between countries, with some countries currently lacking any effective approach.

Where pricing and payment models are flexible enough to allow implementable price reductions for the constituent parts of combination therapies, the challenge then becomes deciding what value/price is appropriate for each constituent part of a combination. This involves consideration of *how* the value/price should be determined, and *who* should determine the value/price.

Options for 'how' value is attributed between constituent parts of a combination therapy have been briefly discussed in the literature,[2,13] as described in the workshop pre-read paper.[7] Simple options exist (for example, splitting the revenue equally). An alternative is to develop a formal quantitative value attribution framework, where value and price is set based upon the estimated benefit that each constituent part contributes to the combination – though this may not be straightforward to calculate and an accompanying expert deliberative process factoring in relevant clinical and scientific information may be needed. The meeting heard a presentation proposing an approach whereby the value of the add-on therapy as a monotherapy is estimated, and then the ratios of the values of the treatments as monotherapies is used as a basis for attributing value to the combination. Danko *et al.* state that valuation methods used in financial markets could be investigated to derive the value of constituent parts, and for linking the added value of the add-on therapy to the 'underlying asset', but do not discuss this suggestion any further.[2] Alternatively, an

expert deliberative process based on relevant clinical and scientific information may be used alone, without quantitative analysis.

Various possibilities exist for 'who' should be responsible for all or part of the value attribution process. HTA agencies or payers could, for example, take responsibility for developing or commissioning research on appropriate quantitative methods; could take a lead in setting up and running an expert deliberative process (which might include manufacturers and which may or may not incorporate a developed quantitative framework), or; could invite/require manufacturers of the constituent parts of a combination to set up and run a deliberative process themselves. Manufacturers could fund or commission research on appropriate quantitative methods; could join an expert deliberative process being run by HTA/payer bodies; could develop and run their own expert deliberative process, or; could rely on case-by-case ad-hoc undefined solutions.

Competition law and anti-trust legislation places legal constraints on what manufacturers can and cannot do. Legal experts present at the workshop explained the issues that may arise when separate companies seek to negotiate the prices of constituent parts of a combination therapy. Issues involving competition law and (potentially) price fixing have serious implications. Some workshop attendees suggested that the situation may be helped by the participation of a third party, in the form of an HTA agency or payer – suggesting that these agencies may have an important role in the value attribution process. This echoes suggestions made in the literature by Danko *et al.*, who state that only bilateral negotiations between the payer and each individual owner company would be lawful, with the intention of avoiding direct negotiations between companies.[2] Meeting attendees were also told about a trading platform that has been designed to enable companies to trade, without meeting, under the supervision of HTA agencies. However, legal experts explained that the involvement of HTA agencies and payers in price negotiations between companies may not solve the legal problems. In some circumstances it may raise additional issues. The possibility of obtaining agreement from a competition authority for a "safe harbour" arrangement for companies to negotiate with each other was discussed. What is permitted, however, may differ in different jurisdictions. This is critical, and dictates whether price negotiations offer a practical solution to the challenges associated with providing affordable access to effective combination therapies.

Notwithstanding the legal issues, the role that HTA/payer bodies feel able to play may be constrained by their formal remits or concerns about what is appropriate for them to take responsibility for, which is likely to depend on the type of system that the HTA/payer body operates within. Some may feel that they have a role to play in determining the value of specific treatments and/or in ensuring that action is taken to facilitate patient access to beneficial treatments. Others may feel that their remit is only to assess the value of the overall combination package, with the prices of the constituent parts of the combination a commercial issue for manufacturers to address.

It should be noted that, if one company manufactures all of the constituent parts of a combination therapy, price negotiation is much less of an issue, because all revenue goes to the same manufacturer and that manufacturer has control of the price of the entire combination package. A price acceptable to the payer must still be arrived at but negotiations involve only one company, simplifying the process. When more than one company manufacture different parts of the combination, negotiation and value attribution may become more problematic, and that is when the issues described above are likely to arise.

Incentives for companies to take part in negotiations are also important to consider. In particular, if a backbone therapy exists and is in use, and a new add-on therapy is developed, it is questionable whether the manufacturer of the backbone therapy has incentives to enter into price negotiations – as highlighted by Persson and Norlin.[13] In principle, patient access to the combination therapy will increase the volume of sales of the backbone therapy. However, if negotiations are likely to result in a reduced price being set for the backbone therapy the company may see limited gain from negotiating. Workshop attendees considered whether HTA agencies or payers had an ethical responsibility to play an intermediary role in the negotiation process, if companies would not (or could not) negotiate acceptable prices on their own. It was suggested that if HTA assessment of a new add-on therapy triggered a re-assessment of the backbone therapy – and possible disinvestment in this – the manufacturer of the backbone therapy may be incentivised to negotiate.

How could this be achieved?

Workshop attendees generally agreed that when previously provided monotherapies are combined and produce clinical benefit that is not proportional to the combined price, it would be appropriate for prices to be re-visited. Similarly, when new add-on therapies are combined with an existing backbone therapy and provide clinical benefit, it is appropriate for the price of the backbone therapy to be re-visited.

For implementation, workshop attendees felt that the exact method used to implement a price reduction in any combination use was relatively unimportant, but that it was important for an adequate system to be in place to support it. Workshop attendees felt that it was important for HTA agencies and payers to communicate clearly with manufacturers to determine what type of flexible pricing model is acceptable to achieve price reductions for combination uses in their jurisdiction. Importantly, it was highlighted by several attendees that any flexible pricing mechanism is likely to require good data on the use of cancer treatments, including clinical indication, therapy line, type of combination, dosing and treatment duration. Alternatively, reasonable assumptions about differential use of treatments would need to be made based on epidemiological data. In areas where sufficient data collection or information systems do not exist, these would need to be developed. Importantly, workshop attendees also highlighted that in private insurance-based systems, or in areas where patients make co-payments for medical treatments, flexible payment systems that involve rebates paid at a health system level could be problematic for patients who might not get their fair share of any rebate in terms of reduced co-payment or cost share.

Workshop attendees felt that research into how value could be attributed between constituent parts of a combination therapy would be valuable. The outcome of this research could act as a starting point for negotiating prices. Multiple stakeholders should be involved in this research – HTA agency and academic involvement in methods development may increase its credibility and make adoption more likely. In addition, attendees stated that however value attribution is done, it should be done early in the HTA process – ideally before submission for reimbursement to HTA agencies or payers – to avoid delays in the appraisal process, which would delay access to patients.

Workshop attendees differed in their views of who should be responsible for attributing value to the constituent parts of a combination therapy. Some attendees felt that this was the responsibility of the pharmaceutical companies involved – HTA representatives suggested that HTA agencies and payers are responsible for assessing the value of overall treatment packages, not the individual

constituent parts of a combination treatment. Other workshop attendees felt that value attribution was a natural role for HTA agencies and/or payers, because their remit was to assess the value of healthcare interventions. Attendees also pointed out that there was an important distinction between HTA agencies and payers: payers may wish to specify acceptable prices for constituent parts of a combination therapy whereas this may be less important for an HTA agency.

There was wide agreement that HTA agencies/payers had – at least – an important facilitation role. This may involve providing legal assurance that price negotiation in this context is in the interests of the public good – thus, potentially, providing a legal basis under competition rules for price negotiations between companies to take place. Or, the HTA agency/payer may seek to facilitate discussions which result in the relevant competition/legal authority indicating a position on the legality of any negotiations, without the HTA agency/payer openly supporting any particular legal position. This will depend upon the local laws in the jurisdiction in which the negotiation takes place. Workshop attendees strongly agreed that there was an urgent need for pharmaceutical companies and HTA agencies/payers to explore the legalities of price negotiations between companies (possibly with the involvement of HTA agencies and payers) in different jurisdictions around the world.

Workshop attendees also felt that it was important for all stakeholders to consider how companies (particularly manufacturers of backbone therapies) could be incentivised to participate in price negotiation – though little time was available for this at the Bellberry workshop. Workshop attendees pointed out that often prices are confidential – manufacturers of one constituent part of a combination therapy may not even know the price of another constituent part. Moving from this to a price negotiation process represents a large step.

Attendees pointed out that companies would sometimes be the manufacturer of the backbone therapy, and would sometimes be the manufacturer of the add-on therapy, and therefore, with this in mind, should approach negotiations openly and considering the implications across their portfolio, perhaps using a rules-based approach to attribute value between constituent parts of a combination. It was also noted that even if the unit price of backbone therapy was reduced, revenue for the manufacturer of the backbone therapy may be sustained, or even rise, if the addition of the add-on treatment resulted in the backbone therapy being used for longer. Views were also expressed that suggested a hope that pharmaceutical companies would be willing to negotiate on price if their treatment remained part of a new treatment regimen that provided clinical benefit – since doing so would be appropriate from an ethical perspective.

In addition, attendees pointed out that the potential for re-assessment of (and possible disinvestment in) backbone therapies by HTA agencies or payers could act as an incentive for manufacturers to negotiate. Indeed, workshop attendees felt that when combination therapies were assessed and issues arose regarding the value for money of existing backbone therapies, this should trigger a re-assessment by HTA agencies/payers of the backbone therapy (potentially leading to a price cut for these).

Finally, workshop attendees also considered as an alternative to price negotiation the re-development of a combination therapy as one combined product (for example, given in one pill, or one injection), as suggested by Persson and Norlin.[13]. Workshop attendees felt that this would frequently be practically and scientifically impossible due to the make-up of different compounds in the combination. In addition, there was a strong feeling that such an approach would be highly

inefficient – as it would involve substantial amounts of time and money being invested in re-developing exact copies of treatments that already exist. Also, with the existence of patents, negotiation between companies would still be required and thus this approach would do little to solve any of the issues associated with negotiating prices of the constituent parts of combination therapies. As an alternative, companies may decide to develop their own version of the backbone therapy – this version would not be an exact copy, but would be as close as possible without contravening the patent of the existing backbone therapy. This may avoid negotiation between companies, but is still inefficient because substantial amounts of time and money would be being invested in developing treatments that are intentionally similar to those that already exist.

7. Additional issues identified during the public meeting

In Section 6 we have, where possible, incorporated discussion that occurred during the public meeting held on Day 3 of the Bellberry workshop. However, one additional issue was identified that does not fall into any of the three buckets discussed in Section 6, yet represents an important area in the context of making clinically effective combination therapies available to patients.

A member of the audience highlighted the issue that occurs when combination therapies made up only of off-patent (and therefore low cost) treatments are shown to be clinically effective but do not become available to patients because they lack an interested sponsor company to initiate a change in the license for the constituent therapies, or to initiate the HTA/reimbursement process. As a result, these combination therapies may not become recommended for use. Such treatments may well represent very good value for money for health systems due to their low cost. The problems with valuing and paying for these combination therapies are therefore different to those discussed in the rest of this report. Whilst such combinations could still benefit from improved clinical trial design (Bucket 1), issues around price and price negotiation are likely to be removed, because these treatments are highly likely to be cost-effective due to being off-patent. Workshop attendees recognised this to be an important issue with serious ethical implications. Manufacturers, regulators, HTA agencies and payers should give this issue further consideration. It is a particular example of what may be termed “repurposing” - developing new clinical uses for “old” drugs. There is a challenge for licensing bodies and for HTA bodies and payers as to how to find a proxy sponsor in such circumstances when there is good clinical evidence of effect. Proposals have been made as to how this could be addressed.[16,17] Meanwhile consortia are working to identify and test “repurposed” drugs.[18]

8. Conclusions

The 3-day Bellberry Workshop involved detailed discussion around crucial issues relating to valuing and paying for combination therapies in cancer. Workshop attendees agreed that, in the situation where two or more on-patent drugs are involved, combination therapies in cancer present important problems for affordability and value for money – and hence patient access – in health systems all around the world,. The aim of the workshop was not to form concrete recommendations or to make consensus statements. However, there was a significant level of support for several different actions associated with improving patient access to clinically effective but high-cost combination therapies (though, support for these was not necessarily unanimous). These actions are listed below, where relevant highlighting which stakeholders would have responsibility for taking the next steps:

a) Thought should be given to the treatment regimens tested in clinical trials. Adaptive and platform trials may be useful practically and from an ethical perspective. Combined scientific advice processes should be considered to enable this, including all relevant stakeholders (e.g. different **HTA agencies, payers, regulators, patients, clinicians, ethicists, academics**).
b) Research is required to identify the most patient-relevant outcome measures to be included in clinical trials. This requires input from **all stakeholders.**
c) **Manufacturers and HTA agencies/payers** should work to make more use of post-launch studies and real world data to provide information on alternative treatment regimens.
d) There is not currently a case for altering HTA decision rules or deliberative frameworks specifically for combination therapies.
e) When combination therapies are assessed by **HTA agencies/payers** and issues arise regarding the value for money of existing backbone therapies, this should trigger a re-assessment of the backbone therapy by the **HTA agency/payer**.
f) Attempting to re-develop combination therapies as a single product is inefficient, often impossible, and faces many of the same challenges that it is intended to overcome. Having the manufacturers of add-on therapies try to develop “me-too” versions of backbone therapies is also very inefficient.
g) **Manufacturers** should revisit the price of backbone therapies (in respect of their use within the combination) when add-on therapies are combined and provide clinical benefit, with a view to ensuring that the price of the combination therapy is commensurate with its value whilst also allowing prices for constituent parts that are acceptable to their manufacturer. Similarly when existing monotherapies are combined.
h) It is important for **HTA agencies and payers** to communicate clearly with **manufacturers** to determine what type of flexible pricing model is implementable to achieve price reductions in their jurisdiction.
i) **Health systems** need to have in place appropriate systems to collect data on the actual or likely use of cancer treatments, if flexible pricing and payment mechanisms are to be used.
j) There is a range of views on who (**manufacturer, HTA agency, payer**) should be responsible for attributing value to the constituent parts of a combination therapy. This needs to be discussed and agreed within specific jurisdictions.
k) **HTA agencies/payers** have – at least – an important facilitation role in enabling price negotiation.
l) There is an urgent need for **manufacturers, payers and HTA agencies** to explore the legalities of price negotiations between companies in different jurisdictions around the world.
m) Research – involving **all stakeholders** – into how value could be attributed between constituent parts of a combination therapy would be valuable.
n) It is important for **all stakeholders** to consider how to incentivise companies (particularly manufacturers of backbone therapies) to participate in price negotiations.

o) It is important for **pharmaceutical companies, regulators, HTA agencies and payers**, to further consider how to provide patient access to low-cost combination therapies that are newly found to be clinically effective, in the absence of a manufacturer sponsor to take them through the regulatory and HTA processes. This is not an issue relating directly to high cost combination therapies, but one that is potentially important to improving the quality of cancer care through new uses for off-patent medicines.

Actions a) to n) represent a path forward in the process of enabling patient access to clinically effective but high-cost combination therapies for cancer. Each stakeholder has a role to play and many issues must be addressed. More discussion is required within specific jurisdictions to agree on an action plan and allocate actions to different stakeholders to ensure progress is made. Collaboration between all stakeholders is required if the necessary steps are to be taken. It is hoped that this report will provide a template for such discussions.

It appears that improved clinical development and design, and flexible pricing and payment mechanisms represent the two key options for helping ensure appropriate patient access to clinically effective combination therapies in cancer. Improving clinical development programmes and trial design represents an important step but will take time to achieve. Ensuring that pricing and payment mechanisms are flexible represents a more immediate option – though this too may take time to implement.

Fundamentally, there is an urgent need for pharmaceutical companies, HTA agencies and payers to further explore the legal challenges associated with price negotiation between companies, to ensure that an appropriate framework for discussions can be established in specific jurisdictions around the world. Furthermore, flexible pricing needs to be implementable within health systems. In addition, once health systems are set up to allow price negotiation and flexible pricing, mechanisms for attributing value between constituent parts of combination therapies will be needed – so research on possible methods is important. Without price negotiation and flexible pricing, the problems associated with valuing and paying for combination therapies in cancer will not be solved.

In tandem, it is crucial for all stakeholders to work on improved trial design to provide evidence on optimal treatment regimens that increase benefits to patients and reduce costs to health systems. By improving the combination therapies and regimens being developed and by allowing flexible pricing and negotiation, the challenges associated with valuing and paying for combination therapies in cancer can be addressed.

9. References

1 Humphrey, R.W., et al., *Opportunities and Challenges in the Development of Experimental Drug Combinations for Cancer.* Jnci-Journal of the National Cancer Institute, 2011. 103(16): p. 1222-1226.

2. Danko, D., J.Y. Blay, and L.P. Garrison, *Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology.* Health Policy, 2019.

3. Davis, S., *Assessing technologies that are not cost-effective at zero price.* NICE Decision Support Unit, Sheffield, 2014.

4. The National Institute for Health and Care Excellence, *Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel): appraisal consultation document.* 2013, The National Institute for Health and Care Excellence: London, UK.

5. Fleeman, N., et al., *Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer*. 2013, LRiG, The University of Liverpool.

6. PBAC Public Summary Document: PERTUZUMAB, 420 mg/14 mL injection, 1 x 14 mL vial Perjeta®, Roche Products Pty Ltd. The Pharmaceutical Benefits Scheme, Australian Government, Department of Health. March 2014. [Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-03/pertuzumab]

7. Latimer N, Pollard D. Pre-read document 1: Challenges in valuing and paying for combination regimens in oncology, School of Health and Related Research, University of Sheffield, 6th November 2019. [Available from: https://www.sheffield.ac.uk/scharr/sections/heds/discussion-papers/20_02-1.882458]

8. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Medicine; 16;29; 2018

9. Schiavone F, Bathia R, Letchemanan K, Masters L, Amos C, Bara A et al. This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols. Trials; 20;264; 2019

10. Hague D, Townsend S, Masters L, Rauchenberger M, Van Looy N, Diaz-Montana C et al. Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons. Trials; 20; 294; 2019

11. Morrell L, Hordern J, Brown L, Sydes MR, Amos CL, Kaplan RS. Mind the gap? The platform trial as a working environment. Trials; 20; 297; 2019

12. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 [Available from: http://www.nice.org.uk/article/pmg9/chapter/foreword]

13. Persson, U. and J.M. Norlin, *Multi-indication and Combination Pricing and Reimbursement of Pharmaceuticals: Opportunities for Improved Health Care through Faster Uptake of New Innovations.* Applied Health Economics and Health Policy, 2018. 16(2): p. 157-165.

14. Towse, A., A. Cole, and B. Zamora, *The Debate on Indication-Based Pricing in the US and Five Major European Countries*, in *OHE Consulting Report*. 2018, Office of Health Economics: London.

15. Mestre-Ferrandiz, J., et al., *Seminar Briefing 18: Multi-indication Pricing: Pros, Cons and Applicability to the UK.* , in *Office of Health Economics: Research*. 2015, Office of Health Economics: London.

16. Association of Medical Research Charities. Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice. 2017, Association of Medical Research Charities:

London [Available from: https://www.amrc.org.uk/blog/facilitating-adoption-of-off-patent-repurposed-medicines-into-nhs-clinical-practice]
17. Pushpakom S, Iorio F, Eyers PA, Jane Escott K, Hopper S, Wells A *et al.* Drug repurposing: progress, challenges and recommendations. Nature Reviews Drug Discovery; 18, 41-58; 2019
18. Queensland Drug Repurposing Initiative, Centre for Clinical Research, The University of Queensland, Australia. Information available from: https://clinical-research.centre.uq.edu.au/qdri

10. Annex 1: List of attendees, day 1 and day 2 of the Bellberry workshop

Name	Job Title	Institution
Niklas Hedberg	ChiefPharmacist/Chair Executive Board	TLV/EUnetHTA
Dan Ollendorf	Chair , HTAi Policy Forum	Tufts Medical Center USA
Andrew Wilson	Chair PBAC	University of Sydney
Robyn Ward	Chair MSAC	University of Sydney
Adriana Platona	First Assistant Secretary	Dept Health Canberra
Brian O'Rourke	President & CEO	CADTH Canada
Thomas Lonngren	Independent Strategy Advisor	PharmaExec Consulting AB Sweden
Nick Simpson	Medical Advisor	Dep Health,Canberra
Andrew Mitchell	Advisor HTA	Dep Health Canberra
Amanda Adler	Chair Technology Appraisal Committee	NICE UK
Jacoline Bouvy	Senior Scientific Adviser	NICE, UK
Daphne Khoo	Deputy Director of Medical Services	Ministry Health,Singapore
Dr David Danko	Managing Partner	Ideas and Solutions,Budapest,Hungary
Dr Meena Okera	Medical Oncologist and PBAC Member	Adelaide Cancer Centre,Australia
Prudence Scott	Medical Oncologist and Director	Medex Consulting. Australia
Prof Rosalie Viney	Director, Centre Health Economics and Research Evaluation	University Technology Sydney
Prof Kirsten Howard	Professor of Health Economics	University of Sydney
Prof Wolfgang	Professor of Health Economics	Universitat Bielefeld Germany
Ann Single	Chair HTAi Patient and Citizen involvement	Australia
Karen van Gorp	Consumer Advocate	Melanoma Patients Australia
John Stubbs	Consumer Advocate	Australia
Jo Watson	Deputy Chair PBAC	Dept Health,Canberra
Jake Lebiecki	Senior Director, Market Access Methods	Pfizer
Gergana Zlateva	Integrated Team Lead for Market Access and HEOR,	Pfizer
Louise Graham	Head of Market Access	Pfizer
Duncan O'Brien	Head of Integrated Market Access	Janssen
Brandon Jones	Senior Health Economics Manager	Janssen
Joice Valentim	Global Health Systems Strategy Lead	Roche
Carlene Todd	Market Access and Public Policy Director	Roche
Brenda Pote	Associate Director, Market Access	Roche
Andrew Bruce	Director Health Policy	Amgen
Anusha Kheir	Exec Dir Global Health Economics	Amgen
Mickael Lothgren	Exec Director, Global Health Economics	Amgen
Shunya Ikeda	Health Economist	International University of Health and Welfare,Japan
Elizabeth de Somer	CEO	Medicines Australia
June Challen	Senior Pharmacist, Investigational Drugs	Queen Elizabeth Hospital ,Adelaide
Amy Shelly	Head of Research Governance & Optimal Care	Cancer Council, Victoria
Ian Kerridge	Haematologist & Ethicist	University of Sydney
Margo Somerville	Professor Bioethics School of Medicine	The University of Notre Dame,Sydney
John Hill	Board Director	Bellberry
Malcolm Crompton	Board Director	Bellberry
Fraser Bell	Chair, Bellberry Director	Bellberry
Dr Chris Henshall	Independent Consultant	London UK

Dan Pollard	Research Associate ScHARR	University of Sheffield
Kylie Sproston	CEO	Bellberry
Lloyd Sansom	Director	Bellberry
Nicholas Latimer	Reader in Health Economics ScHARR	University of Sheffield
Leanne Weekes	Programme Director	CT:IQ Australia
Carla Deakin	Programme Director	NICE UK
Jerneen Williams	Early Phase Clinical Trial Manager	Bellberry
Adrian Towse	Emeritus Director	Office of Health Economics, UK
Simon Ellis	Senior Associate	Clayton Utz
Mihkel Wilding	Special Counsel	Clayton Utz