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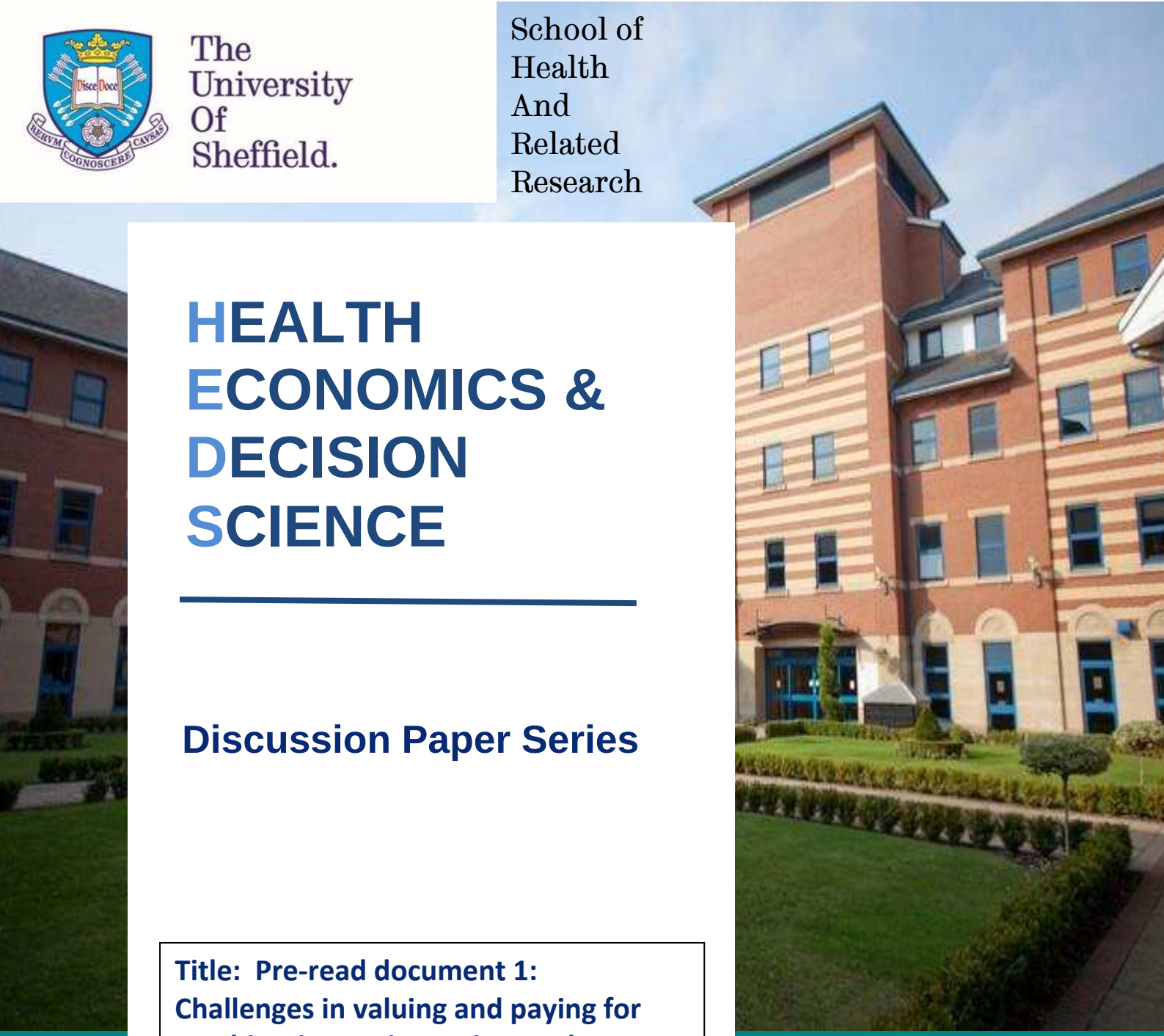

HEALTH ECONOMICS & DECISION SCIENCE

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Title: Pre-read document 1: Challenges in valuing and paying for combination regimens in oncology

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Pre-read document 1: Challenges in valuing and paying for combination regimens in oncology

Pre-read document for an international workshop convened by Bellberry held on November 18-20, Sydney, Australia

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1. Abstract

This document was prepared as a pre-read paper for people attending an international workshop convened by Bellberry, Ltd. The workshop was held to discuss the challenges in valuing and paying for combination regimens in oncology. Cancers often arise through multiple biological mechanisms, meaning that treatments that target only one of these mechanisms may not provide long lasting benefit to patients. Therefore, it is common to treat cancers with multiple 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. This pre-read document introduces and illustrates the challenges associated with combination therapies, considers how different approaches used by health systems to determine whether new treatments should be paid for may affect these challenges, and presents a review of options for addressing these challenges, with the aim of facilitating debate on how best to ensure patient access to clinically effective combination therapies.

2. Introduction

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 depend on many altered molecular pathways and multiple mechanisms of immune resistance. 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 become common for combination treatments to be used to treat many cancers, and this is highly likely to continue in the future. In this paper, we present a summary of the challenges associated with valuing and paying for combination regimens in oncology.

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 a 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 'product', and consider whether the value of the product 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 combined product, 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 price of the combination product.

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 overall product, and which also

provides the producer with a return that they deem acceptable. Indeed, it has been claimed that in health systems that use cost-effectiveness assessment, add-on therapies are usually found to be not cost-effective – sometimes even when the add-on therapy is allocated a zero price [3].

From a societal health perspective this is problematic, because as long as a new combination therapy provides clinical benefit compared to existing therapy, there should exist 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 overall product being acceptable to the payer. This suggests that one approach to addressing some of the challenges associated with valuing and paying for combination regimens in oncology is communication and negotiation between producers of the constituent parts of a combination therapy. However, this itself raises issues around:

- *Value attribution*: if companies are to negotiate (or if a payer were to re-set the price that they are willing to pay for the backbone therapy), how should value be attributed to the constituent parts of the combination therapy?
- *Remit*: if value is to be attributed to the constituent parts of the combination therapy, who has the remit to estimate the value attribution?
- *Legal challenges and competition law*: to what extent are companies permitted to negotiate a combined price for a combination treatment?
- *Implementation*: if the price of the backbone therapy is changed when used in combination, then different prices may be needed for different uses of the backbone therapy (often called multi-indication or indication based pricing)

These issues represent some of the obvious challenges associated with trying to ensure an efficient use of combination treatments in cancer. However, it is possible that other challenges – and options for addressing these challenges – have already been discussed in the literature. To provide a comprehensive summary of issues associated with valuing and paying for combination regimens in oncology we conducted a review of the literature and conducted a simple survey of invitees to the Bellberry meeting. The remainder of this paper has 7 sections. In Section 3 we provide three hypothetical examples outlining the kinds of issues that may arise when add-on therapies are developed. In Section 4 we give an example of the extreme “not cost-effective at zero price” scenario. In Section 5 we consider how different approaches used by health systems to determine whether new treatments should be paid for may affect the issues associated with valuing combination regimens. In Section 6 we present our review of the literature. In Section 7 we present additional information on multi-indication pricing – which represents an important component of several of the approaches identified for trying to ensure an efficient use of combination treatments in cancer. In Section 8 we present the results of our survey undertaken on invitees to the Bellberry meeting and in Section 9 we discuss our findings.

3. Hypothetical Examples

The following hypothetical examples are provided to stimulate thought about some of the issues that may arise when considering valuing and paying for new add-on therapies. They are purposely simple, consider benefit only in terms of overall survival, and use length of overall survival as the only variable in the scenarios.

Box 1: Hypothetical Examples

1. Drug A is registered as monotherapy for a specific cancer and represents standard care, representing backbone therapy. Drug A is priced to the maximum level at which the payer or HTA agency is willing to permit reimbursement. Drug B is developed as an add-on therapy for the same indication, only to be given in combination with Drug A. No data are available for Drug B as monotherapy.

   Drug A monotherapy provides overall survival of 6 months
   Combination A+B provides overall survival of 8 months

   The incremental benefit of the combination therapy is 2 months, and therefore for the combination therapy to be considered 'good value' the price of Drug B combined with Drug A must be commensurate to an incremental benefit of 2 months. Given the price of Drug A, and because Drug A must be given in combination with Drug B in every additional month of survival gained, this means that a low price must be set for Drug B. If the company who produce Drug B is not willing to provide Drug B at the price required to achieve reimbursement then the combination will not be available.

   - Consider how to deal with this situation if: (a) the same company produces Drug A and Drug B; (b) different companies produce Drug A and Drug B.
     - How could the company(ies) respond?
     - How could the reimbursement agency/payer respond?

2. Drug A is registered as monotherapy for a specific cancer and represents standard care, representing backbone therapy. Drug A is priced to the maximum level at which the payer or HTA agency is willing to permit reimbursement. Drug B is developed as an add-on therapy for the same indication, only to be given in combination with Drug A. No data are available for Drug B as monotherapy.

   Drug A monotherapy provides overall survival of 2 months
   Combination A+B provides overall survival of 8 months

   The incremental benefit of the combination therapy is 6 months, and therefore for the combination therapy to be considered 'good value' the price of Drug B combined with Drug A must be commensurate to an incremental benefit of 6 months. Given the price of Drug A, and because Drug A must be given in combination with Drug B in every additional month of survival gained, this means that a low price must be set for Drug B. If the company who produce Drug B is not willing to provide Drug B at the price required to achieve reimbursement, then the combination will not be available.

   - Consider how to deal with this situation if: (a) the same company produces Drug A and Drug B; (b) different companies produce Drug A and Drug B.
     - How could the company(ies) respond?
     - How could the reimbursement agency/payer respond?

3. Drug A and Drug B are registered and reimbursed as monotherapy in the same disease population. A value of benefit is known for each drug (compared to best supportive care (BSC)) and appropriate prices have been agreed commensurate with the magnitude of benefit. Subsequently, the combination of A+B is tested.

   Drug A monotherapy provides an overall survival benefit of 6 months compared to BSC
   Drug B monotherapy provides overall survival benefit of 4 months compared to BSC
   Combination A+B provides overall survival benefit of 8 months compared to BSC

   Hence, the benefit of the combination is less than the sum of the constituent parts.
   Benefit (A+B)<(Benefit A + Benefit B)

   The price of the combination therapy now has to be assessed against the benefit of the monotherapies, and to be considered 'good value' the price of the combination will need to be less than the existing price of Drug A + Drug B. If prices are not changed, the combination therapy will not be made available.

   - Consider how to deal with this situation if: (a) the same company produces Drug A and Drug B; (b) different companies produce Drug A and Drug B.
     - How could the company(ies) respond?
     - How could the reimbursement agency/payer respond?

4. "Not cost-effective at zero price"

The Decision Support Unit (DSU) for the National Institute for Health and Care Excellence (NICE) published a report in 2014 setting out scenarios in which clinically effective technologies may be found not to be cost-effective even if they are zero priced.[3] One of the scenarios in which this may occur is when new therapies are added on to an existing backbone therapy. The full report is provided as an additional pre-read document. Here we briefly summarise the case of pertuzumab 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. Again, the intention is to stimulate thought about the issues associated with valuing and paying for combination treatments.

Box 2: Not cost-effective at zero price: Pertuzumab for metastatic breast cancer

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients 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 represent the backbone therapy, and pertuzumab represents the add-on therapy. Treatment with pertuzumab and trastuzumab should continue until disease progression or unmanageable toxicity.

The NICE Appraisal Committee was satisfied 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.[6, 7]

The DSU calculated that the annualised cost associated with remaining in PFS was £27,253, even when assuming a zero price for pertuzumab. 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 a supportive care cost.

Assuming no difference in post-progression survival between the backbone therapy and the combination therapy, the cost-effectiveness analysis simplifies to a trade-off between the QALY gains associated with additional PFS and the acquisition cost of pertuzumab.

Put simply, the cost of a 1-year increase in PFS was calculated to be £27,253, and thus the cost of the 6 month PFS gain attributed to the pertuzumab combination was £13,627, even if pertuzumab had zero price. 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 £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). Hence, 1 additional year of PFS is worth 1*0.785 = 0.785 QALYs, and a 6 month gain is worth 0.393 QALYs. Therefore, the incremental cost per QALY gained for the combination therapy for the 6 month PFS gain is £13,627/0.393 = £34,712, even if pertuzmab had zero price.

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, if its clinical benefits are limited to extending PFS.

It is clear to see that this issue arises due to the cost of the backbone therapy, but is also affected by the quality of life experienced in the extended period of life. If the quality of life associated with PFS was perfect (i.e. the utility score was 1.0), there would have been some 'headroom' and pertuzumab could have been considered cost effective at a price greater than zero. Conversely, if the utility score associated with PFS was lower, pertuzumab would have been even further from being cost-effective even with zero price. This demonstrates that if the backbone therapy itself is priced to be cost-effective up to the threshold, or is priced above this so is not cost-effective, then, by definition, any therapy that is added to this will not be considered cost-effective, even if it delivers clinical benefit.

This example is useful to consider when thinking about hypothetical ways in which the company (or companies) and the reimbursement agency could have responded to this situation.

The DSU report discusses three alternative approaches to appraising treatments which are not cost-effective at zero price. These are summarised below:

i) *Defining costs incurred during added life-years as being unrelated*. It is the assumption of most HTA bodies that costs unrelated to the technology being appraised can be excluded from the cost-effectiveness analysis. If costs incurred solely due to increased survival can be classified as unrelated, then it may be argued that these could be excluded from the analysis, providing more 'headroom' for the pricing of the add-on therapy. Such an argument could be made for best supportive care costs – such as those of the backbone therapy. However, the DSU report states that *"it is hard to see how the health gains associated with care provided alongside the technology of interest with the same treatment intent can be considered to be unrelated to the health gains attributable to the technology of interest".*[3] In addition, the DSU report states that excluding some healthcare costs has implications for the allocation of healthcare resources as a whole, as it may result in less cost-effective treatments being reimbursed, to the detriment of the system as a whole as more cost-effective treatments are displaced. In fact, the DSU report suggests that if an add-on therapy is considered not cost-effective at zero price, NICE may wish to consider dis-investing from the background intervention (i.e. the backbone therapy).

ii) *Properly accounting for benefits.* The DSU report states that it is important to ensure that all benefits of treatments are taken into account. In particular, it is important to ensure that quality of life has been appropriately estimated, and that benefits to carers have been taken into account (especially when palliative care costs are high – presumably representing good quality care which may reduce distress in carers). It is also suggested that there may be instances where "QALY weights" could be applied, if it is considered that societal preferences are not captured within the health benefits already included in the QALY.

iii) *Ethical reasons for accepting a higher ICER.* The DSU report suggests that even if a life-extending treatment was not considered cost-effective at zero cost, a NICE Appraisal Committee could still consider recommending the treatment if it felt there were ethical reasons to do so – in line with the NICE Social Value Judgment policy.

It is relevant to note that none of these issues are specific to combination therapies – rather they are focused on any intervention that might be considered not cost-effective at zero price. We will refer back to these options in our Discussion, in Section 9.

5. Do the issues raised by combination therapies differ according to the approaches taken to assessing value and determining 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, given that the price of the add-on therapy must take into account the price of the backbone therapy, and price must be commensurate to the therapeutic value of the product. These issues also 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.

6. Literature Review

Search strategy

The aim of our review was to identify issues associated with valuing and paying for combination regimens in oncology that have been identified and discussed in the literature. Reviews of methods or issues are different to reviews of clinical studies, and therefore different searching approaches are required – standard PICO (Population, Intervention, Comparators, Outcome) criteria make little sense. We adopted a "pearl growing" technique in an attempt to identify relevant articles.[8] This process involved three steps:

1. Identify one or more "pearl" papers. Conduct a citation and reference search using these papers
2. MEDLINE search using a set of specific search terms based on key words and terms based upon the pearl paper(s)
3. Search of the references in papers included after steps (1) and (2)

We used a paper published by Humphrey *et al.* as our pearl paper.[1] This paper was published in 2011, summarising a session on "Developing experimental drug combinations: opportunities and challenges" held at the Melanoma Research Alliance Annual Scientific Retreat held in February 2010 in Las Vegas, US, and seemed a particularly relevant precursor to the Bellberry workshop. Humphrey *et al.* discussed opportunities and challenges in the development of combination treatments for cancer, focussing mainly on the conduct of clinical studies and regulatory approval, without considering how combination therapies might be valued.[1] A brief summary of the Humphrey *et al.* paper is provided in Box 3.

For pragmatic reasons we only searched for articles that were published in the last 10 years (i.e. published after 2009) which were published in English. We included papers that considered either theoretically or practically the valuation of combination therapies in cancer. Obviously many papers have been published assessing the value or cost-effectiveness of combination treatments, but these were only included in our review if they also addressed challenges associated with valuing or paying for these treatments. The search terms used for our MEDLINE search are presented in Table 1.

Table 1: MEDLINE search strategy

#	Searches
1	((combine or combined or combination*) adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or melanoma*) adj5 (drug or therap* or treatment*)).ti.
2	(reimbursement or fourth hurdle or pay* or health technology assessment or price or pricing or value or fund* or economic*).tw.
3	1 and 2
4	limit 3 to (english language and yr="2009 -Current")

To supplement our pearl growing search we undertook a search of the International Society of Pharmaceutical and Outcomes Research (ISPOR) and Health Technology Assessment International (HTAi) presentations databases, in an attempt to identify any relevant work that has not been published in peer reviewed journals. We searched these databases using the terms "value or reimbursement or pricing" and "oncology or therap*" and "combination".

To further supplement our searches, we searched the reference lists and citations of any articles that we determined to meet our criteria. One reviewer (DP) assessed whether the included articles met the inclusion and exclusion criteria. The results were synthesised narratively.

Box 3: Summary of Humphrey et al. (2011). Opportunities and challenges in the development of experimental drug combinations for cancer

Humphrey *et al.* state that combination therapies represent an important approach for treating cancer, but note that most new cancer drugs are developed as single agents – though we note that whether this remains true is unclear. The authors identify several reasons for a continued focus on single-agent treatments, and the majority of the paper is focused on clinical development and clinical trial design. However, they also refer to challenges that are relevant for the pricing and valuation of combination treatments, particularly when agents are developed by multiple institutions or companies. These include:

- Economic considerations harming productive collaborations
- Contracting and intellectual property issues

Although these issues may be seen as barriers to the production of combination treatments, the authors state that partnerships between companies using risk sharing and profit sharing business models, as well as between sectors (academia, industry and government) can leverage resources and mitigate risk.

In fact, the authors state that whilst legal issues are often cited as barriers to the development of combination therapies, in reality there are very few true legal barriers. The authors state that tensions around patent, regulatory and transactional dynamics are sometimes expressed in legal terms – implying that these issues are actually not legal in nature. However, importantly, here the authors are referring to the legalities of jointly developing a combination treatment, rather than bringing to market a combination of two treatments developed separately. Indeed, Humphrey *et al.* state that other "*sources of possible contention include the division of expenses and profit, proposals for exclusive arrangements, disagreements about commercial strategy, and the complexity of combination product pricing*."

The authors do not offer any specific solutions to these issues around pricing and profits, where anti-trust considerations are likely to be crucially important. However, they do note that: "*In general, the greatest barrier to agreement on combination therapy is the desire of one party to extract more value from the partnership than is warranted by its contribution to the collaboration. This potential barrier results when the negotiation is viewed as a zero-sum exercise, with an economic winner and a loser. However, collaborations can create added value for each partner*"

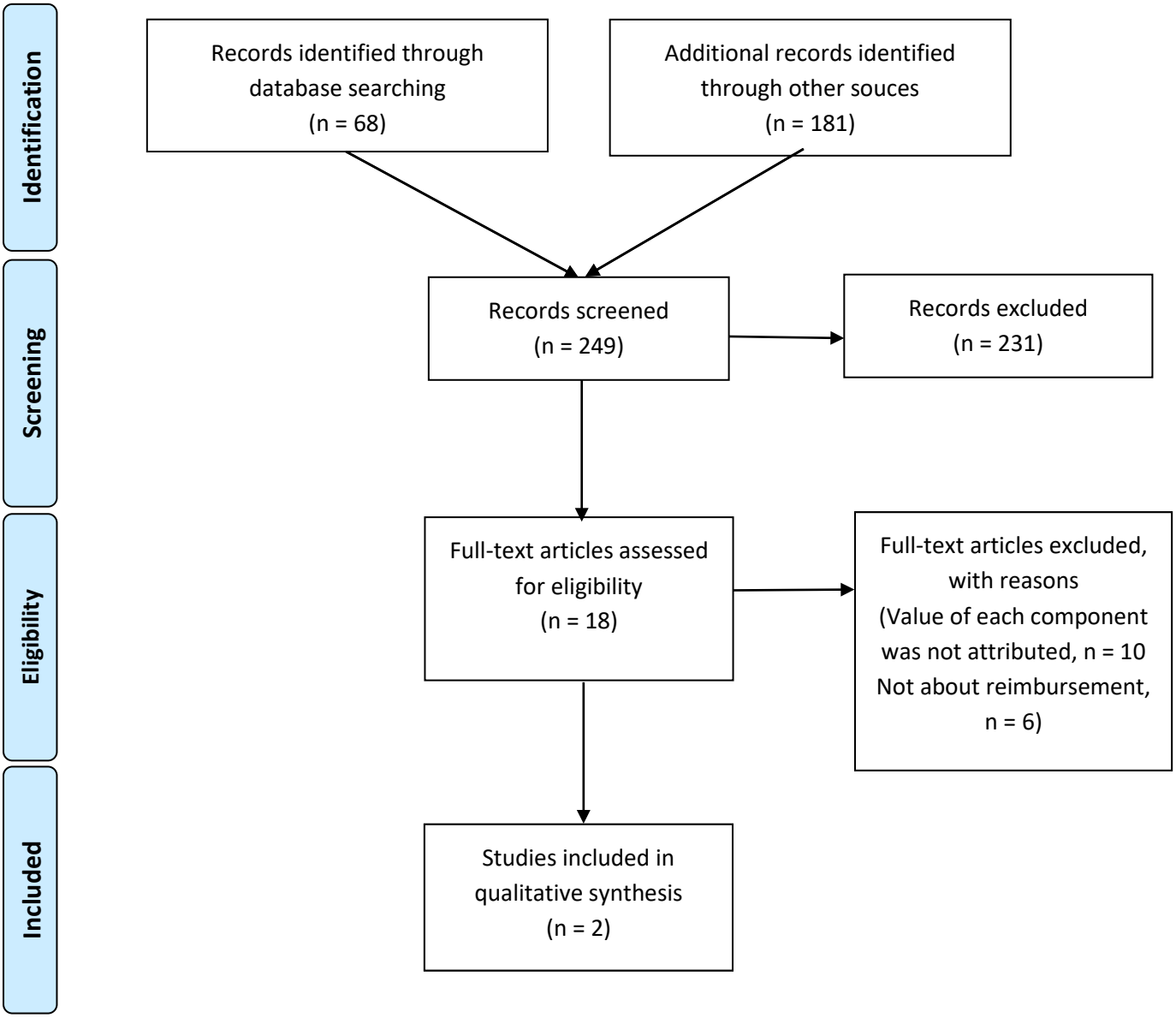
Search results

Our initial searches found 104 articles that were either referenced by Humphreys *et al*. or cited Humphrey *et al*.[1] A further 68 articles were identified through our MEDLINE search. Finally, 77

articles were identified in the reference lists or cited the included articles from the pearl and MEDLINE searches.

This left 249 articles to assess. 231 articles were rejected during the title or abstract sifting, leaving 18 full text articles to be assessed. 16 of these articles were rejected, the most common reasons being: either the paper didn't propose how to attribute value between the two components of the combination therapy (n = 10), or the paper was not about the reimbursement of combination therapies (n=6). This left two full text articles that were relevant to this review, one by Danko *et al* [2] and the other by Persson and Norlin.[9] The information in this paragraph is summarised in a PRISMA flow diagram for study selection, presented in Figure 1.

Figure 1: The PRISMA flow diagram



Our searches of the grey literature found 19 potentially relevant conference abstracts presented at ISPOR or HTAi in the last 3 years (2017 to 2019). Of these 19 conference abstracts, 6 were relevant to our review [10-15]. In addition to the solutions proposed by Danko *et al.* and Persson and Norlin, only one additional option for assessing the value of combination therapies was identified, described in two abstracts by Ratcliffe *et al*.[2, 9-11]. As such we only consider these two abstracts in addition to Danko *et al.* and Persson and Norlin in our narrative synthesis.

Narrative Synthesis

Overview

Danko *et al.* state that combination therapies in oncology pose a budget challenge to health systems, and an economic return challenge for companies developing them[2]. The authors, who were funded by an unrestricted grant from Amgen, conducted a literature review to identify challenges specific to combination therapies and also reviewed relevant reports published by HTA and pricing and reimbursement bodies. This paper is therefore highly relevant for the Bellberry meeting, and is included as Pre-read document 4.

Persson and Norlin, who received funding from Janssen-Cilag, consider multi-indication pricing and combination pricing of pharmaceuticals in the context of value-based pricing in Sweden[9]. The authors focus mainly on situations where the value of a drug differs in different indications, and how this might be addressed to allow patient access to effective drugs at efficient prices. Combination treatments are not the sole topic of the paper, but the authors offer potential options for addressing the pricing issue in the context of combination therapies.

Ratcliffe *et al.* present a pair of conference abstracts investigating HTA decision making for combination oncology therapies covering five European countries (Italy, France, Germany, Sweden, and the UK)[10]. The funding source for this work is not stated. The authors consider whether positive reimbursement decisions are attainable for combination therapies, and suggest potential options for increasing the likelihood of positive reimbursement decisions.

Danko *et al.,* Persson and Norlin and both Ratcliffe *et al* abstracts identify issues associated with the reimbursement of combination therapies in oncology.[2, 9-11] Danko *et al.* state that in health systems that apply cost-effectiveness assessment (Canada, England, Scotland, Sweden) add-on therapies are usually deemed not to be cost-effective, sometimes even at zero price, due to the incremental direct costs of constituent therapies.[2] The authors state that positive funding decisions are contingent on price discounts and managed entry agreements. The authors do not describe what these managed entry agreements entail, but state that current frameworks for such agreements are applicable only when the constituent therapies have the same owner. Persson and Norlin also cite examples of where add-on therapies have been deemed not to be cost-effective, even at zero price.[9] Danko *et al.* state that where HTA is focused on added clinical benefit (France, Germany), most concerns associated with the reimbursement of new add-on treatments are around clinical study design, tolerability, lack of proven benefit and the adequate efficacy of monotherapy.[2] From this it may be inferred that the issues are essentially the same as in systems that apply cost-effectiveness assessment – primarily, the clinical evidence is not strong enough to provide confidence that the add-on treatment represents good value for money. Danko *et al.* state that payers seem unable to manage the conflicting incentives of different owners of constituent

therapies, and that no specific mechanisms exist for attributing added clinical benefit to the constituent therapies[2]. In sum, Danko *et al.* conclude that sub-optimal reimbursement of combination therapies will lead to health system losses[2]. Ratcliffe *et al.* state that whilst positive reimbursement decisions are possible for combination treatments in systems that explicitly consider clinical and cost-effectiveness (cited as the UK and France), positive decisions are more likely in systems with more flexible decision-making criteria (cited as Germany, Sweden and Italy).[10]

Danko *et al.* construct a 'problem map', in an attempt to distil and link each issue associated with valuing and paying for combination therapies [2]. Below, we use categories identified by Danko *et al.* and summarise the authors' discussion of these, where relevant adding in material from Persson and Norlin and both Ratcliffe *et al* conference abstracts, as well as adding in our own commentary [2, 9]. Throughout, the recommendations made by the authors of the reviewed papers for addressing the challenges associated with valuing and paying for combination therapies are highlighted in italics for ease of reference.

Value recognition and willingness-to-pay

Danko *et al.* start by acknowledging that health care systems have restricted budgets and therefore cannot pay for all treatments[2]. The authors state that a challenge to the reimbursement of combination therapies for oncology results from the fact that payers have in general shown no willingness to increase their willingness-to-pay threshold for these treatments. The authors suggest that ***differentiated willingness to pay (WTP) thresholds should be explored*** in order to address the budgetary constraint issue[2]. The authors acknowledge that this may be controversial, but suggest that such an approach could be rational if longer term benefits accrue, through encouraging future innovation, or if it is accepted that it is necessary to fight cancer through multiple pathways. However, the authors base this recommendation on an assumption that there exists a societal preference to invest more in combination treatments for cancer than in monotherapies, or in other non-cancer treatments, without providing any evidence suggesting such preferences exist. Where the cost-effectiveness threshold represents opportunity costs, increasing the threshold for one type of treatment means that treatments with lower cost-effectiveness ratios are squeezed out of the system, resulting in overall societal losses. Ratcliffe *et al.* state that the Swedish HTA approach, which allows variable cost-effectiveness thresholds according to therapeutic area and disease severity offers a more flexible approach for determining cost-effectiveness – but it is unclear whether treatments would be afforded a higher cost-effectiveness threshold in the Swedish system simply for being part of a combination therapy [10, 11]. Linked to this, Ratcliffe *et al.* suggest that the German system of HTA, involving the use of an "efficiency frontier", avoids the use of explicit thresholds and potentially offers more scope for combination cancer therapies to be reimbursed [10, 11].

Danko *et al.* also state that the magnitude of benefit offered by combination treatments is not always captured appropriately [2]. They note that systems that focus on therapeutic added value (e.g. France, Germany) may rely on median estimates of survival which do not adequately reflect the skewed survival distributions that may result when small proportions of patients achieve long term survival. Further, the authors state that systems that rely on cost-effectiveness analysis (e.g. UK, Sweden, Poland) do not capture benefits such as the value of hope. The authors suggest that ***value assessment frameworks that consider broader value concepts could be explored.*** The acceptability

of such an approach is likely to depend upon the perspective taken by payers in health systems around the world. Ratcliffe *et al*. take this suggestion one step further and suggest that decision making may use ***multi-criteria decision analysis (MCDA)***, which would consider multiple criteria within the same formal framework [10, 11]. The authors refer to the Italian system, where there is no fixed cost-effectiveness threshold and decision-making is based on multiple criteria – however, they note that this approach has led to concerns around the transparency in decision making [10, 11].

Pricing

Danko *et al.* state that when add-on therapies are found to be clinically effective but not cost-effective, it may be considered that this is because the cumulative price of the backbone therapy and the add-on therapy is not proportional to the cumulative health gain [2]. The authors state that this is related to inefficiencies in managing the prices of backbone therapies. If the price of the backbone therapy is not revisited, the add-on therapy may be denied funding or the owner of the add-on therapy may be required to reduce its price in order to achieve reimbursement. Danko *et al.* state that this means that the added value of the combination treatment is not properly attributed to the constituent therapies, with most of the allowable price of the combined product being absorbed by the backbone therapy. The authors do not state why this particular value attribution is not appropriate, however it is clear that when a combination treatment does offer a clinical benefit compared to the backbone therapy alone, there should be a price at which the combination treatment can be offered which would represent a cost-effective use of health care resources. If the price of the backbone therapy prevents this, it is logical to ***consider re-visiting the price of the backbone therapy***, as suggested by Danko *et al.* and Persson and Norlin [2, 9].

Danko *et al.* and Persson and Norlin raise several issues that challenge the use of price negotiations between owners of constituent parts of combination therapies [2, 9]:

- **Legal constraints**. When the constituent parts of a combination therapy have different owners, price negotiations between these owners would need to take place if this is requested by payers. Danko *et al.* state that such negotiation is currently restricted by anti-trust/competition law, with these laws meaning that any direct or indirect negotiation between owners is not permitted if market structure or pricing are affected [9]. Therefore, Danko *et al.* state that only bilateral negotiations between the payer and each individual owner are lawful. Hence, the authors suggest that ***price negotiations may need to be led by payers*** [2]. Danko *et al.* also state that ***safe harbour clauses for price re-negotiation will be necessary in anti-trust/competition law*** to allow any price negotiations to take place [2].
- **Flexible payment mechanisms**. If price negotiations were to form part of the assessment of add-on therapies, Danko *et al.* state that payment mechanisms would need to be flexible. The authors state that rebates and budget caps are commonly used (outside of the United States), and these could be used to effectively reduce the price of constituent parts of a combination treatment [2]. Persson and Norlin recognise that ***when the constituent parts of a combination therapy have the same owner, then price-volume agreements between the manufacturer and the payer could be made for the combination use***, but when the constituent parts have different owners combination pricing becomes challenging [9]. Danko *et al.* recommend that ***indication-based or combination pricing must be permitted in order to operationalise a system that allows price negotiation for combination therapies*** [2, 9]. Such pricing mechanisms require that health systems can collect data on

clinical indication, therapy line, type of combination, dosing, and treatment duration or make reasonable assumptions about differential use of the products.

- **Value attribution**. Value attribution mechanisms do not exist, and therefore owners of the constituent parts of a combination therapy may struggle to come to an agreement on the price of their products. Danko *et al.*[2] state that ***value attribution mechanisms are needed***, and that these could either be built into existing HTA processes, or – competition/anti-trust law permitting – negotiation-based systems could be considered.

Persson and Norlin provide alternative examples of possible payment and pricing systems to address the case of a combination therapy that is not deemed good value for money at the prices charged by the owners [9]. These options are presented as alternatives to multi-indication pricing:

- ***Limited payment schemes***. The authors consider a case where the expected survival associated with all constituent parts of the combination therapy when given as monotherapies is known. The full price could be paid for each constituent part of the combination therapy up to the expected treatment duration when given as monotherapy. In all additional months of survival during which treatment is given, the constituent parts could be provided free of charge.
- ***Marginal cost pricing of the backbone therapy***. Price the backbone therapy equal to the marginal cost of producing the good when it is used in combination therapies. The authors suggest that this might be considered "fair" because the owner of the backbone therapy receives its revenue from the value it brings as a monotherapy, whereas the owner of the new drug must bear all the investment cost in the development of the combination therapy. It should be noted that this is a form of multi-indication pricing, rather than an alternative to it.

Persson and Norlin recognise that the owner of the backbone therapy may not agree to the lower price for its product when used in combination with newer drugs, and that in any case the combination pricing of products may lead to legal challenges [9]. This leads the authors to conclude – in line with Danko *et al.* – that if price negotiation is to be operationalised, three-party agreements with payers are needed [2].

<u>Product re-development</u>

Persson and Norlin suggest that a potential solution to the challenges associated with valuing and paying for combination treatments is to ***re-develop the combination as one combined product*** [9]. In such a case a "product-based" assessment (i.e. an assessment considering only the total product rather than its constituent parts) would be straightforward. The prices of the constituent parts of the combination given as monotherapy would not be affected, because a new product would have been developed. This may also lower administration costs, increasing the likelihood that the product could be deemed cost-effective. However, as noted by the authors, it may not be possible to combine some combination therapies into one single product: dosing regimens or the method of administration may differ. The authors do not note that such product re-development would also require substantial collaboration between owners of the constituent parts of the combination, but this is likely to represent an additional barrier to such an approach. In fact, it may be more likely that companies will try to develop their own version of the backbone therapy, so that they can produce the entire combination themselves. This risks a substantial amount of time and money being spent "re-developing" existing drugs, in order to license "me too" versions.

7. Further Detail on Multi-indication Pricing

It is clear that multi-indication pricing represents an important component of several of the options described in Section 6 for addressing issues associated with the valuation of combination therapies. In Box 4 we provide a summary of multi-indication pricing. More detail is provided in Pre-read Documents 5 and 6, by Towse *et al.*[16] and Mestre-Ferrandiz *et al*.[17]

Box 4: Summary of multi-indication based pricing

Multi-indication pricing (or "indication based pricing") refers to the practice of allowing distinct prices to be set for the same product when used in different indications. Since it is frequently the case that new medicines are licensed for more than one indication, and the value the medicine generates in each indication will be different, it has been argued that indication based pricing promotes wider access to medicines whilst remaining consistent with standard approaches to value assessment, and thereby also encourages drug development.

In the context of combination therapies, the concept of indication based pricing is relevant not only where medicines have multiple indications, but also where they have different uses within the same indication, that is as either backbone, monotherapy or as add-on as part of a combination. If differential prices are permitted depending on use, this becomes an important component that provides greater flexibility in determining the range of acceptable and feasible prices for the component parts of a combination.

Indication based pricing may be challenging in practice since it requires information on volumes of usage by indication, or assumptions of predicted utilisation data based on epidemiological data in order to arrive at a single weighted average price across indications. It may be even more complex for health systems to identify use within an indication. There must be no, or negligible opportunities for arbitrage (purchasers to buy at the lower priced use and resell for use in the higher priced use).

8. Survey of Invitees to the Bellberry Meeting

Emeritus Professor Lloyd Sansom emailed all invitees to the Bellberry meeting asking for comments on the following issues:

a) What you see as the 3 key issues and challenges that combination regimens raise for assessment of the value and the reimbursement of oncology drugs, and what you see as the key solutions/ways forward
b) If you are engaged in, or aware of, any current work on solutions-theoretical and/or practical-to the challenges raised by combination regimens

We received 5 responses, provided by oncologists, HTA policy experts, researchers, and industry representatives. The issues and challenges identified were:

1) Methods for attributing benefit and harm from each constituent part of the combination therapy and using this to set prices for each constituent part.
2) Constituent parts have different owners which limits collaboration – for example trial data and pricing information may not be shared, but should be.
3) Balance of slightly improved effect versus a greatly increased toxicity. Respondent suggests the owner of the treatment should pay for side-effect management.
4) Prediction of effect of combination therapies, so that they are only used when the benefit is likely to be greater than the harm. Respondent suggests that pharmacogenomics of predictive genomics may represent a solution for this.
5) Propensity for regulators to approve new combination regimens on a "treat to progression" basis, lengthening the potential duration of treatment and lessening the chance that fixed-cycle treatment approaches will be tested in future. Respondent suggests that regulators could insist that companies study the impact of fixed-cycle treatment or drug holidays.
6) Adding a new component to a multi-drug regimen that itself is cost-ineffective, removing the likelihood that the new drug will be cost-effective at any price. Respondent suggests that a potential solution is for the pharmaceutical industry to engage in package pricing across products and companies to achieve cost-effective combined product prices.
7) The relative absence of company-collected data on the quality-of-life impact of new treatment combinations—in other words, a lack of data to inform whether additional progression-free survival or overall survival is manageable from a toxicity standpoint
8) Lack of useful comparator evidence: the new combination should be compared to the backbone therapy and the backbone therapy's comparator regime.
9) Challenges associated with valuing and paying for combinations when the clinical data is immature, particularly in the context of accelerated registration processes.
10) Legal challenges associated with the pricing of constituent parts of a combination therapy in a value attribution framework setting.
11) Challenges associated with combination treatments that do not involve drug combinations and may not involve concurrent treatment. For example, when a treatment pathway involves drug treatment and surgery, or a test is followed by, or used in the course of, treatment with one or more drugs.

Issues (1), (2), (6), (9) and (10) involve challenges around value attribution, negotiation, clinical data and legal issues already established in our review of the literature – though an important additional point around the quality of immature clinical data in the presence of accelerated regulatory approvals is made. Issues (3), (4) and (7) relate to concerns about quality of life issues associated

with combination therapies, though they may also relate (to a greater or lesser extent) to oncology drugs in general. Quality of life is clearly a very important factor when considering combinations of toxic therapies, but is routinely taken into account by HTA agencies and payers around the world. Therefore this should not represent an issue that is not currently adequately addressed in the assessment of combination therapies. Issues (5) and (8) relate to the evidence typically provided in clinical trials of combination therapies, suggesting that current clinical development programs do not routinely assess the most efficient use of new combination regimens, and that sufficient evidence on comparators is often not collected. Issue (11) highlights that challenges associated with combination therapies do not only arise when medicines are given concurrently – many other treatment pathways include combinations of therapies. We refer back to the issues identified by this survey in our Discussion, in Section 9.

9. Discussion

It is clear that combination therapies are increasingly common in cancer, and it is highly likely that combination therapies will continue to be developed, given the underlying nature of cancer and strategies for treating it. As with any treatment, there will be an overall cost or a price set for a combination therapy at which it would be deemed cost-effective, or good value for money, given the benefits it delivers. Agreeing on the nature and value of those benefits can be a challenge with any treatment, but combination therapies present some specific challenges for HTA agencies and payers, particularly where a new treatment is added to an existing backbone therapy that has been priced to take full account of the value that it may deliver on its own. In that situation, a commercially viable price for the new therapy may be impossible to agree unless either there is increased willingness to pay for the benefits actually delivered by the combination, and/or the price of the backbone therapy is re-negotiated. Both these approaches raise further challenges for HTA and payment systems and/or for manufacturers.

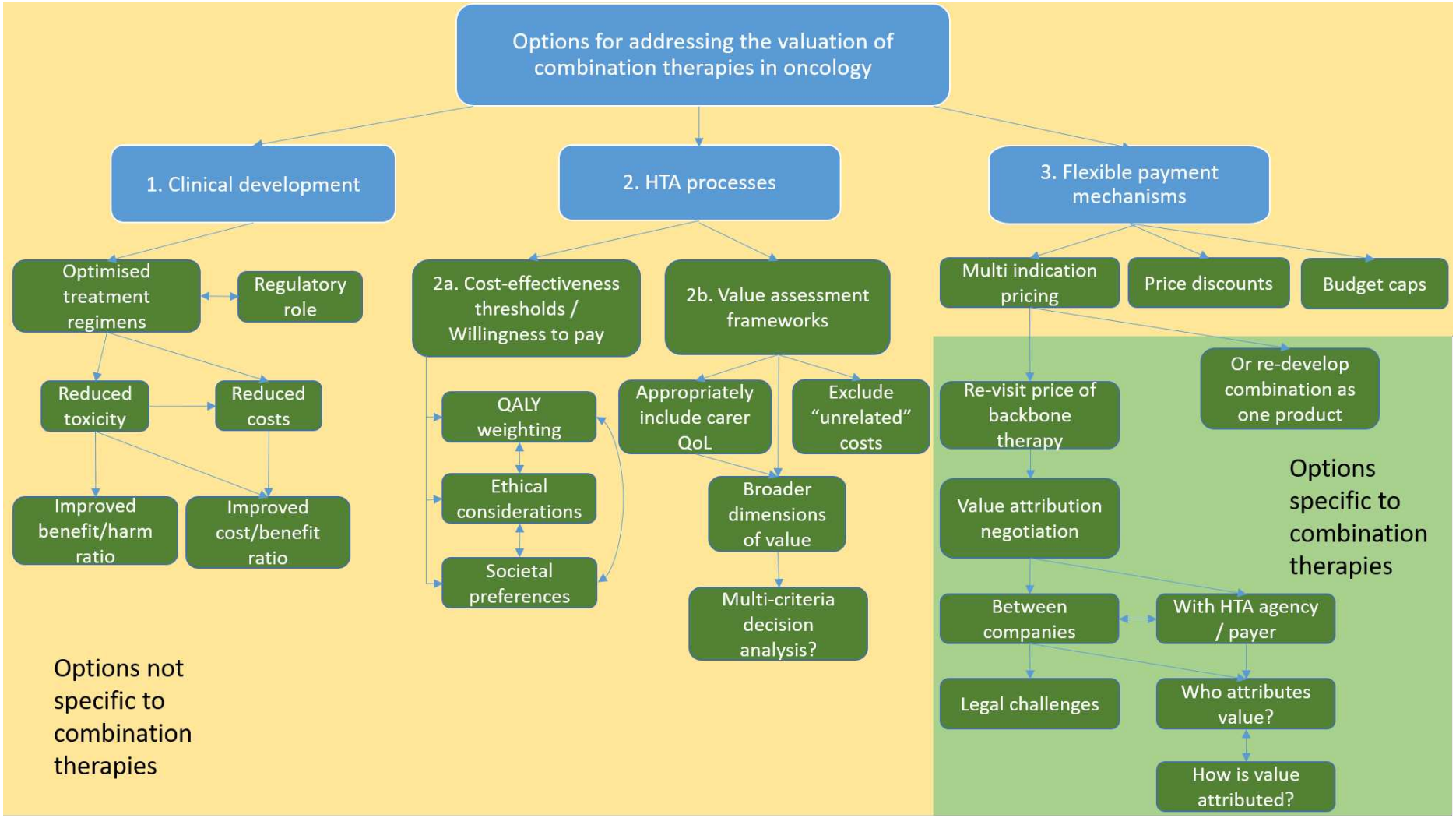
Options identified from the literature to address the specific challenges of combination therapies, and additional options identified by our survey of invitees to the Bellberry meeting, are listed below:

1) Higher cost-effectiveness thresholds / willingness-to-pay thresholds or QALY weighting for combination treatments
2) Modifications to value assessment frameworks, for example to include wider dimensions of value, and/or exclude certain types of cost
3) Flexible payment mechanisms
4) Re-visit the price of the backbone therapy, or, in the extreme, disinvestment in backbone therapies that are not considered cost-effective or good value for money
5) Value attribution mechanisms
6) Re-development of combination therapies as one combined product
7) Optimised treatment regimens

In our opinion, options (2), (3) and (7) are not specific to combination therapies. Options (2) and (3) could in principle be implemented by payers or HTA agencies more widely, and option (7) is an issue to do with clinical development and treatment registrations that is relevant for any new therapy. Option (1) is related specifically to combination therapies here, but it too could be considered more widely, as in the Swedish system. Options (4) to (6) are options that are specific to combination therapies, but fall within the broader category of (3) – flexible payment mechanisms, which could consist of discounts, multi-indication pricing or budget caps.

In Figure 2 we attempt to summarise the options for addressing the valuation of combination therapies in oncology, their interconnections and key implications. We split the options into three broad categories – clinical development; HTA processes, and; flexible payment mechanisms.

Figure 2: Options for addressing the valuation of combination therapies in oncology: Interconnections and key implications



Category (1), which encompasses clinical development issues, was identified through our survey of invitees to the Bellberry meeting. Meeting invitees were concerned about the toxicity of combination treatments and believed that methods should be developed to attempt to predict when and for whom the benefits of combination therapy would outweigh the harms. Related to this, it was suggested that combination treatment regimens routinely investigated in clinical trials may not represent the most efficient use of these regimens. In cancer, combination therapies are usually given until disease progression, but the respondents to our survey suggested that if shorter treatment durations were tested in clinical trials, they may result in a similar clinical effect together with reduced costs and toxicity. Hence, by optimising treatment regimens – both in terms of dose and treatment duration, and with respect to attempting to identify *who* should be treated (perhaps with individual-specific doses/regimens) – some of the challenges associated with paying for combination therapies could be diminished. These considerations also relate to ethical challenges associated with combination therapies (and with cancer therapies in general). Our review of the literature identified little discussion around ethical issues, but these do exist and are not out of scope for discussion at the Bellberry meeting.

The options within Category (2), around HTA processes and encompassing value assessment frameworks and cost-effectiveness thresholds, require changes to the way that health care interventions are assessed in most countries around the world. For option 2a (altering cost-effectiveness thresholds for combination treatments) to represent a realistic option in many systems, evidence would need to be provided that societal preferences are such that there is a desire to pay more for combination cancer treatments than any other treatments (including mono-therapies for cancer). At present such evidence does not exist. If societal preferences were not in favour of paying more for combination cancer treatments, then increasing the willingness-to-pay/cost-effectiveness threshold for these treatments in systems with fixed budgets would result in societal losses through lost health due to disinvestment in other health care interventions. However, as noted by the DSU report on treatments that are considered not cost-effective at zero price,[3] in some circumstances it may be considered that there is an ethical need to provide a treatment despite a very high cost-effectiveness ratio.

The acceptability of option 2b (altering value assessment frameworks) is likely to depend on the perspective currently taken by the HTA agency or payer in question and the scope and rationale for flexibility within it. Again, if changes are proposed only for combination therapies in oncology, a justification would presumably be required for that. One component of this option that is unlikely to be controversial, and which was specifically identified in the aforementioned DSU report, is the inclusion of impacts on the quality of life of carers.[3] It is acceptable in NICE appraisals to include quality of life benefits associated with carers but often this is not done, or is not done appropriately. In particular, where supportive care costs are high and treatment is effective, it may be expected that the quality of life of the treated individuals' loved ones also increases. Defining who is a "carer", how many carers patients have, and estimating quality of life gains for carers is not straightforward, but it appears that in this respect, the full benefits of effective treatments are not currently being routinely incorporated into value assessments.

Category (3) includes options that are more specific to the issues raised by combination therapies, and require some type of flexible pricing to be possible. In reality, it seems likely that this category contains the most realistic approaches for addressing the challenges associated with achieving

reimbursement for more combination therapies. It seems fundamental that if the combination therapy provides clinical benefit, but the price of the existing backbone therapy precludes the combination being offered at a combined price that is acceptable to the HTA agency / payer, some degree of negotiation around the price of the backbone therapy is essential. If the constituent parts of the combination therapy have the same owner, this should be relatively straightforward without any substantial changes to existing payment systems, because price-volume agreements could be used.

The situation is much more complex if the constituent parts of the combination therapy do not have the same owner. Anti-trust and competition law may preclude price negotiation between owners, with both Danko *et al.* and Persson and Norlin suggesting that payers (or, presumably, HTA agencies) leading three-way discussions.[2, 9] As originally suggested by Humphrey *et al.*, negotiations between owners are likely to be problematic as each company attempts to maximise its return, making agreement difficult to achieve.[1] Respondents to our survey of invitees to the Bellberry meeting felt that pharmaceutical companies should be willing to make combination pricing agreements in order to provide clinically effective combinations at prices that are acceptable to health systems. In reality, it seems possible that the owner of a backbone therapy may be unwilling to negotiate on its price in order to achieve reimbursement as part of a combination therapy, particularly if the alternative is for the backbone therapy to continue to be given as monotherapy. However, this ignores the fact that when given as part of a combination therapy the backbone treatment may be given for longer, potentially providing higher revenue even with a lower price. In addition, it is likely that over time companies will find themselves on both sides of the transaction – sometimes producing the backbone therapy and sometimes producing the add-on treatment. Hence, it would appear to be in the economic interests of all companies to be open to price negotiations.

If pricing negotiations between companies were to be pursued, perhaps with the payer or HTA agency as an intermediary, it is likely that some form of multi-indication pricing would be required. This raises many practical issues of its own, and Persson and Norlin suggest that such schemes are challenging to implement.[9] Detailed information on prescribing of drugs would be required, which could lead to considerable administrative burden. However, in some health systems administrative data may exist to facilitate this. For example, the Systemic Anti-Cancer Therapy (SACT) dataset collects considerable amounts of data on the use of anti-cancer treatments in England.[18]

If pricing negotiations between companies were to be pursued, facilitated by some form of multi-indication pricing, a method for arriving at agreed prices for the constituent parts of the combination therapy is required. One option is to leave this to the owners of the constituent parts to negotiate, using whatever approaches they see fit. An alternative is to adopt a formal value attribution mechanism administered by the HTA agency or payer as part of the value assessment of the combination product. A third option is for the payer or HTA agency to oversee the negotiations between the companies involved, within the maximum value that it has set as the value of the combination therapy. Danko *et al.* state that valuation methods used in financial markets may 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] Respondents to our survey of invitees to the Bellberry meeting suggested that methods should be developed to attribute value to constituent parts of combination therapies, and that pricing should reflect this

value attribution. We have not identified any detailed suggestions for how to attribute value amongst the constituent parts of a combination therapy. Potential methods could draw on the effectiveness of constituent parts given as monotherapy – but such information will often be unavailable for some of the components. Hence, further research is required on methods for attributing value to constituent parts of combination therapies.

Re-development of a combination treatment as a single product may seem like a useful approach, but in many cases it is likely to be technically and/or clinically impossible to combine the constituent parts of a combination regimen into a single combined product. And where the intellectual property rights of the constituent therapies is owned by different parties, there would be a need for those parties to come together to agree how the combined product would be produced and marketed and revenues shared. This means that the companies would need to address the same issues around negotiation, but would have less information to come to an agreement, because agreements would be made before the product was developed rather than after. Nonetheless, where this is possible and if multi-indication pricing is deemed impossible (for whatever reason), this option may provide a mechanism for allowing more flexibility in the pricing of the combination product. However, all implementation barriers associated with multi-indication pricing would still need to be overcome and additional legal issues may arise when two separate companies own the combined product. An alternative would be for companies to develop their own “me too” versions of backbone (or add-on) therapies. This may avoid some of the implementation barriers, but large-scale re-development of existing products is unlikely to be efficient.

Conclusions

Challenges associated with valuing and paying for combination therapies in oncology exist around the world. All treatments that provide clinical benefit have a price at which they should be considered good value for money, but it is challenging to arrive at such a valuation and price when drugs are given in combination. Failure to provide combination therapies at an acceptable price results in societal losses, and it is therefore important to consider options for addressing this issue. Several options have been identified but these are not straightforward and are likely to require further development, with input and collaboration from pharmaceutical companies, HTA agencies, payers, clinicians, patients, ethicists and academics. The Bellberry meeting is intended to facilitate this process.

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