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CURRENT OPINION

Assessing the Value of New Treatments for Hepatitis C: Are International Decision Makers Getting this Right?

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Abstract Health systems worldwide are facing difficult choices about the use of a series of highly effective but costly new treatments for hepatitis C. In this paper we discuss how the National Institute for Health and Care Excellence in England and Wales, the Common Drug Review in Canada and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia have approached the appraisal of these drugs. We argue that with the exception of the PBAC, assessments of the new drugs have not adequately accounted for their large financial burden. Given the potential health system impact of reimbursing these drugs, the use of lower cost-effectiveness thresholds should be considered. None of the decision-making processes included a comparison of the full range of treatment pathways. In particular, comparisons of using the new drugs as first- versus second-line drugs were omitted from all appraisals, as were comparisons with delayed treatment strategies whereby treatment is withheld until more severe disease stages. Omission of comparators leads to inaccurate estimates of cost effectiveness and potentially sub-optimal decision making. Lessons learned from these appraisals should be considered in future appraisals, particularly the upcoming assessments of the 'blockbuster' PCSK9 inhibitors for hypercholesterolaemia.

Key Points for Decision Makers

Assessments of the new direct-acting antivirals (DAAs) for hepatitis C have not adequately accounted for the large financial burden placed by these drugs on healthcare systems.

This financial burden implies a large opportunity cost in terms of forgone health. Alternative approaches, such as the use of lower cost-effectiveness thresholds, should be considered.

Appraisals of the new DAAs should compare all available treatment pathways, including use of the new DAAs as first- or second-line treatments and the possibility of delaying treatment.

1 Introduction

Health systems worldwide are currently grappling with the cost of a series of new direct-acting antivirals (DAAs) for hepatitis C. The medicines offer higher cure rates and fewer adverse effects than older medicines; however, their high price tags in combination with the large number of infected patients have generated concerns about affordability. Many countries have begun the process of making reimbursement decisions for these treatments. These decisions will determine which patients can access the DAAs. Developing evidence-based guidance for these treatments has proved challenging due to the changing treatment landscape, limited randomised controlled trial evidence and large number of clinical subgroups. Furthermore, the sheer size of the budget required to implement recommendations is a major source of concern for

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those responsible for freeing up the required resources. For example, NHS England requested that the National Institute for Health and Care Excellence (NICE) delay the requirement for implementation of guidance on one treatment—sofosbuvir—from the normal 3-month timeframe to 6 months [1]. In this paper we discuss how NICE, and comparable bodies in Canada and Australia, are making these decisions. These three Health Technology Assessment (HTA) agencies are well-established and respected for their transparent and rigorous decision-making processes. We assess whether they have got it right when appraising these high-impact technologies. In particular, we discuss (1) how the large costs associated with these decisions should impact decision making; and (2) how the tools of health technology appraisal could be better used to assess the value of the new DAAs.

2 International Funding Decisions

We reviewed publically available documents relating to appraisals conducted by NICE, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Common Drug Review (CDR) in Canada. Documents relating to appraisals conducted in 2014–2015 and published prior to 16 July 2015 were reviewed. In 2014–2015 NICE, CDR and PBAC each have ongoing or completed appraisals for several new DAAs (Table 1). In all jurisdictions, decisions were made on a drug-by-drug basis to speed up access to clinically beneficial treatments.

3 Decision Making for Technologies with a Large Cost Impact

The healthcare investments associated with the new DAAs are predicted to be large. PBAC anticipates a cost impact in excess of 3 billion Australian dollars ($A) over 5 years following its recommendations for sofosbuvir, daclatasvir and ledipasvir/sofosbuvir [2]. NHS England estimated that the cost of NICE guidance for sofosbuvir alone could be £1 billion [3]. This is a large investment as NHS England had a budget of £95.6 billion for 2013/2014 [4]. A recent Therapeutic Review by the Canadian Agency for Drugs and Technologies in Health (CADTH) noted that these treatments "have the potential to significantly affect health system sustainability" [5]. The large predicted cost impacts are a result of the large number of eligible patients and the cost of a course of the new DAAs (with the cheapest in the UK—ledipasvir plus sofosbuvir over 8 weeks—costing approximately £26,000 [6] and the most expensive—sofosbuvir plus daclatasvir over 24 weeks—costing approximately £120,000). The predicted total costs are also very uncertain as it is unclear what impact interferon-free regimens will have on the proportion of patients coming forward for treatment, and whether capacity constraints will limit uptake.

International decision makers vary with respect to whether they consider the cost impact of a technology when making reimbursement decisions. NICE explicitly state that "budget impact" does not determine the Appraisal Committee's decisions [7]. PBAC includes financial impact as part of the decision-making process [8], and in Canada final reimbursement decisions are made by individual drug plans and are likely to consider total cost [9, 10]. This raises the question of how budget impact *should* impact upon decision making. For many decisions new technologies divert only a small proportion of the healthcare budget. To illustrate this, imagine if all funded activity in a health system was ranked in terms of the health delivered per £1000, as shown in Fig. 1 (based on the approach by Culyer [11]). To maximise population health, decision makers invest from left to right until the health system budget is exhausted. In accordance with traditional principles of cost-effectiveness analysis,

Table 1 Appraisals of new direct-acting antivirals in hepatitis C (2014–2015)

Treatment appraised	Status of reimbursement decisions[a]		
	NICE	CDR	PBAC
Asunaprevir	None	Suspended	Complete
Daclatasvir	Ongoing	Ongoing	Complete
Ledipasvir/sofosbuvir	Ongoing	Ongoing	Complete
Ombitasvir/paritaprevir/ritonavir and dasabuvir	Ongoing	Ongoing	Ongoing
Simeprevir	Complete	Ongoing	Complete[b]
Sofosbuvir	Complete	Complete	Complete

CDR Common Drug Review, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee

[a] Status as of 16 July 2015

[b] Change to recommended listing requested

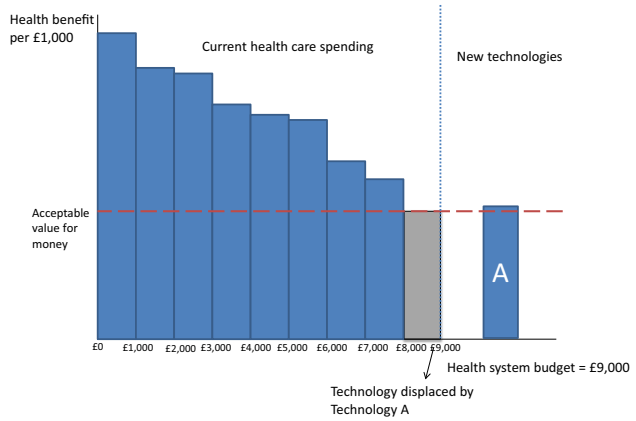

Fig. 1 Opportunity cost of small investments

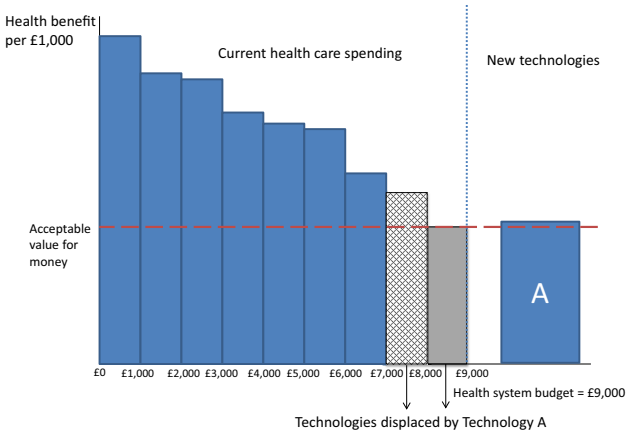

Fig. 2 Opportunity cost of large investments

decision makers should only invest in a new intervention if it generates health benefits per £1000 that are higher than the lowest-value intervention (the marginal programme) currently funded. In Fig. 1, this is represented by comparing the health benefits of technology A (the new intervention) with the health benefits of the marginal programme (shaded grey) that will no longer be offered in order to fund technology A. A cost-effectiveness threshold is typically used to represent the health impact of disinvesting in the marginal programme. In this example, technology A offers more health benefits per £1000 than the marginal programme and should therefore be funded. This decision is not affected by the total budget impact of technology A. This is because technology A imposes a small budget impact and therefore replaces only marginal programmes of the type shown in grey.

Technologies with a large cost impact are unlikely to replace only the marginal programme as the significant investments require additional disinvestment from non-marginal programmes. This is shown in Fig. 2 where Technology A provides the same health benefit per £1000 but has a large cost impact, and so displaces both the grey bar and the white bar. Because the average health benefit per £1000 across both displaced programmes exceeds the health benefit provided by Technology A, investment in Technology A would result in a reduction in total health benefits. This shows that large investments must offer higher health gains per £1000 than smaller investments, or, in other words, should be judged against a lower cost-effectiveness threshold.

There is no evidence that NICE has considered the cost impact of the new DAAs in their decision making to date. Cost impact was raised as a concern by NHS England in the most recent appraisals published by NICE [6, 12, 13]. However, the NICE committees do not appear to have considered the implications this has for estimating opportunity cost. The CDR recommends that decision making regarding the new DAAs at the local level should take into consideration "drug plan and health care system sustainability", though there is no recommendation on how these considerations should modify local-level decision making [14, 15]. In their appraisals, PBAC were acutely aware of the potential health implications of devoting large quantities of healthcare resources to hepatitis C. They advise that their guidance will impose a "large opportunity cost to [the] health care system" and the implication that the cost-effectiveness threshold should be lowered accordingly (from a typical threshold of around $A45,000 to $A15,000 per quality-adjusted life-year) [2, 16–18].

4 Assessing the Value of the New Direct-Acting Antivirals

Decisions about the new DAAs have been made by comparing each new treatment against existing treatments in terms of clinical and cost effectiveness. The majority of the appraisals used a mathematical model to estimate the lifetime health outcomes and costs associated with alternative treatments. All models used a similar approach. Short-term costs and sustained virologic response (SVR, or 'cure') rates associated with treatment were obtained from clinical trials. Long-term outcomes were then generated based on estimates of the impact of SVR status (cured or not cured) on health and health system costs.

As a principle, the value of a new treatment can only be assessed by comparing the value of all ways in which the new and existing technologies can be used to treat a given patient group. Failing to consider the full range of treatment options carries two risks: (1) that a better value option was omitted from the analysis; and (2) that the added value of the new treatment has been misrepresented as it is not

compared to the next best treatment. The appraisals conducted to date omitted relevant existing and new drug combinations and treatment pathways, generating the potential for poor decision making.

4.1 Omission of Relevant Drug Combinations

Relevant drug combinations were omitted as a result of the concurrency of the product launches and the reimbursement agencies' commitment to providing timely guidance. This resulted in a series of concurrent appraisals in which each drug combination was compared against current treatment practice and not against each other. This resulted in multiple drug combinations being recommended as "an option" without clear guidance on which one should be prioritised. For example, currently NICE recommends five alternative treatments as options for chronic hepatitis C caused by genotype 1 virus although these different treatments are not equally effective and cost effective [19–23].

In the UK, there is no way of setting priorities between these drug combinations without a further appraisal process (namely a multiple technology appraisal), even where there are clear effectiveness or cost-effectiveness arguments for doing so. This priority setting is therefore likely to be conducted outside of NICE, either at a national commissioning level by NHS England, by local commissioners or informally by individual clinicians. If prioritisation occurs at the local level, there may be a 'postcode lottery' of access and decisions may be made by bodies with limited resources to appraise the evidence. Patients in Canada face similar risks as CDR recommendations are not binding and participating drug plans retain independent authority over formulary listings. However, CADTH has recently published an updated Therapeutic Review of drugs for hepatitis C in order to support local decision making [5]. This Therapeutic Review includes (non-binding) subgroup-specific treatment recommendations. These recommendations were based on comparative-effectiveness and cost-effectiveness evidence comparing a wider range of drug combinations than were compared in the original individual drug appraisals. PBAC has also been explicit regarding which treatments will be prioritised for funding. Its recent guidance on three of the new DAAs included recommendations against use of previously appraised alternatives: "peginterferon and ribavirin alone and in combination with telaprevir, boceprevir or simeprevir, are no longer cost-effective at the prices currently listed on the PBS" [2]. In this guidance three different new DAAs were recommended alongside a recommendation to the Minister that they be equally priced to reflect an assessment of equal clinical value.

4.2 Omission of Relevant Treatment Pathways

Appraisals by all agencies considered use of the new DAAs and existing treatments at specific points in the treatment pathway. Treatment comparisons were made for patients at different levels of disease severity and with different levels of prior exposure to antivirals. This reflects an assumption that these patients represent distinct and separate subgroups. In reality, a treatment-naïve patient can become a treatment failure, and a patient with mild disease may progress to more severe disease. The way the comparisons are made therefore assumes that clinicians have a one-off opportunity to treat patients. In other words, it assumes that the decision is between treating patients at, for example, the mild stage and not treating them at all. In reality, patients with mild disease could be monitored and treated once they progress to moderate disease severity. However, this was not considered in any of the analyses. Only 10–20 % of those with chronic hepatitis C will develop cirrhosis over a 20-year period [6, 24]. It therefore seems logical to consider an approach whereby patients are monitored and those with worsening disease who are likely to develop cirrhosis are treated, and to compare the value of this approach to treating patients immediately. This could avoid costly treatment of patients who are unlikely to experience substantial ill health from their disease.

A similar logic applies to the sequential use of treatments. In hepatitis C, existing treatment options such as pegylated interferon combined with ribavirin (PR) are relatively cheap and offer reasonable cure rates, particularly for genotype 3 infections (with SVRs up to about 80 % in infections by genotypes 2, 3, 5 and 6) [25]. Progression of chronic hepatitis C to liver disease is also relatively slow, making treatment with two lines of therapy a feasible option for patients with less severe disease [6, 24]. Using an older therapy such as PR up front followed by a new DAA in patients who do not achieve SVR may therefore represent a wise use of scarce resources. SVR rates for the new DAAs are very high, even amongst previously treated patients [25]. Indeed, the most recent European guidance states that available evidence supports similar effectiveness of interferon-free regimens in patients who have not responded to treatment with PR as in treatment-naïve patients [25]. Restricting DAA use to treatment failures could therefore ensure very high cure rates at a fraction of the costs (as only treatment failures would require treatment with the new and expensive DAAs). Despite the potential for delayed treatment and sequential treatment to offer high value, no attempts were made to consider either strategy in the appraisals completed to date.

5 Conclusion

The new DAAs offer high cure rates for chronic hepatitis C and can provide important health benefits. However, their high acquisition cost and the large eligible patient population mean that the new DAAs have the potential to displace significant amounts of healthcare within and outside of hepatitis C. This implies that the new DAAs should be assessed against a lower cost-effectiveness threshold (although there is little empirical evidence on what this threshold should be). This could have significant ethical implications. Individuals with high-prevalence diseases could be denied drugs considered to offer acceptable value for money in the context of lower-prevalence diseases. However, this assumes that prices are fixed. In reality, given the potential revenues involved, it seems likely that drug manufacturers would be willing to offer the price cuts required to achieve reimbursement at a lower threshold. Indeed, such price cuts were recommended in Australia on this basis for a number of the new DAAs.

Both price and the number of individuals treated are likely to vary over time. Prices are likely to change in response to changes to the treatment landscape such as the availability of competitor products or changes to licensed indications. The number of individuals being treated is also likely to change as the prevalent population is gradually cured and awareness of interferon-free regimens widens. This will affect their budget impact and therefore have implications for the cost-effectiveness threshold. Total budget impact as well as price should therefore be considered when assessing the need to re-appraise the new DAAs.

Alternative mechanisms for addressing the large opportunity cost associated with these treatments should also be considered. As the stock of individuals currently infected with hepatitis C is much larger than the number of yearly infections [26], a large budget impact is likely to be felt only in the first few years of introduction. The opportunity cost of financing these drugs could therefore be reduced if costs could be spread into the future [27], using debt financing or other mechanisms [26]. Regardless of the criterion used to determine whether the new DAAs represent value for money, there is a need for future appraisals to widen their scope to compare all ways in which the new DAAs and existing therapies might be used for patient benefit. In this paper we discuss the need for all drug combinations to be compared head-to-head, for any assessments to explicitly recognise that patients can and do receive multiple lines of therapy, to form a treatment sequence, and to include the possibility of delayed treatment. Clinicians and patient groups have strongly resisted restricting access to those who have trialled PR or have more severe disease. The demands of hepatitis C patients must, however, be set against the demands of those patients who are set to lose from the disinvestments required to fund the new DAAs.

Of the three reimbursement bodies we reviewed, only PBAC appears to have explicitly considered the opportunity cost of the large hepatitis C investment decisions and reflected this in its decision-making process. However, we have no basis for assessing whether the modified threshold used by PBAC appropriately reflected the opportunity cost of the investments.

None of the bodies, despite their thorough and well-developed processes, pre-specified the comparisons that should be made appropriately, and important comparators were omitted from all appraisals. Evidence to support head-to-head comparisons may not have been available due to the rapid and sequential nature of the appraisals. CADTH have recently addressed this via their 2015 Therapeutic Review in hepatitis C, which presented new analyses comparing a wider set of drugs head-to-head. In addition, none of the agencies looked at the value of reserving the new DAAs for second-line patients, or of delaying treatment. Omission of comparators leads to inaccurate estimates of cost effectiveness and may have resulted in sub-optimal decision making by all bodies.

Most countries do not apply the type of HTA processes employed by NICE, PBAC and CDR. Pricing negotiations and reimbursement decisions in many countries do, however, make some assessment of clinical benefit and costs. The considerations raised in this paper remain relevant in these contexts. A positive cost–benefit profile may not be sufficient when budget impact is large and decision rules should be adjusted accordingly. In some contexts this may be occurring already. In France, price negotiations consider sales forecasts and size of the target population [28]. In the USA, the Institute for Clinical and Economic Review (ICER) requires that interventions with a short-term budget impact above a certain threshold be subject to greater scrutiny [27]. However, it is unclear whether these approaches will appropriately reflect the value of new medicines and their opportunity cost. For example, the ICER framework uses a price cap for interventions with a high budget impact that does not reflect their clinical value. In all contexts in which clinical benefits and costs are being compared, the full set of relevant comparators must be appraised in order for the best-value treatment pathways to be identified. Regardless of the specific appraisal process, these comparisons should therefore include the possibility of multiple lines of therapy and delayed treatment.

The financial impact of new treatments may in some instances be limited by mechanisms outside of HTA processes. For example, the UK Pharmaceutical Price Regu-

lation Scheme (PPRS) requires a rebate to the NHS from member pharmaceutical manufacturers when NHS expenditure on branded medicines breaches agreed thresholds. Given the sector-wide nature of such agreements, further work would be required to establish how such rebates could and should be reflected in any individual evaluation.

The lessons learned in the hepatitis C appraisals have wider and immediate relevance. A number of 'blockbuster' drugs for hypercholesterolaemia (members of the PCSK9 inhibitor class) are currently entering the market. These treatments are likely to share a number of features with the new DAAs: they are expected to enter the market in rapid succession, be licensed for potentially very large populations and their use could be targeted at a number of points in the treatment pathway. The lessons learned in the hepatitis C appraisals should be heeded in appraisals of these drugs and others.

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