FORMULARY DESIGN, FAIR PRICE AND FAIR ACCESS FOR PHARMACEUTICALS: THE INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW AND OFFICE OF HEALTH ECONOMICS *WHITE PAPER* FALLS AT THE FIRST HURDLE

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Abstract

The release of the White Paper 'Cornerstones of Fair Drug Coverage' represents an impossible attempt to utilize I-QALY based thresholds to make claims for fair prices. It has been conclusively demonstrated that the I-QALY is an impossible mathematical construct as it involves multiplying time spent in a disease state by an ordinal utility value. Given this fact, the attempt by the Institute for Clinical and Economic Review and the Office of Health Economics to propose imaginary fair price estimates as the basis for formulary design is a futile exercise. The purpose of this commentary is to make clear that the White Paper should not be taken seriously; it perpetuates I-QALY modeling which is an analytical dead end.

INTRODUCTION

The Institute for Clinical and Economic Review (ICER) has devoted considerable time and energy to developing a framework, based on the reference case framework of the National Institute for Health and Care Excellence (NICE) in the UK, to provide a community preference-based recommended 'fair price' for pharmaceuticals. Indeed, ICER congratulates itself on having 'contributed significantly' to determining when a drug price aligns with patient benefits. While we might allow this moment of hubris, the fact is that ICER has actually provided a disservice. The manifest failures of the ICER version of the reference case approach has rendered these I-QALY threshold 'fair pricing' activities a waste of time [1] [2] [3]. The case is straightforward: the ICER framework fails the standards of normal science, in particular the failure to recognize the role of fundamental measurement in restricting the application of utility scores to create estimates of quality adjusted life years (QALYs). This is because the utility scores (e.g., EQ-5D-3L) are ordinal measures; to create a QALY by multiplying time spent in a disease by a utility to create equivalent years of perfect health is a mathematical impossibility; hence the term impossible or I-QALY. This destroys, and that is not too strong a term, the reference case I-QALY modeling and the application of mathematically impossible cost-per-QALY thresholds as an input to 'fair pricing' claims.

The recently published White Paper on 'fair' drug coverage, jointly written with the Office of Health Economics (OHE) in London, takes the application of constructed imaginary evidence one step further: fair pricing and access criteria for formulary design [4]. The purpose of this commentary is to point to the absurdity of this approach in formulary decisions.

The trap both ICER and OHE have fallen into is to believe, along with the majority of those involved in health technology assessment, that rather than focus on the discovery of new facts for emerging products to support pricing and access negotiations, they have followed the 'approximate information' approach [5]. This involves evidence creation rather than the application of the standards of normal science in empirical evaluation, hypothesis testing and the discovery of new facts. The approximate information is created by a modelling simulation, driven by assumption that tracks a hypothetical patient population over its lifetime. The key metric is the I-QALY. The model provides estimates of time spent in different disease stages, these are translated to I-QALYs and are aggregated (appropriately discounted) over the lifetime of the hypothetical population. Costs are also assumed. The result is an estimate (hypothetical) of lifetime costs matched to lifetime I-QALYs. These in turn are matched to the same estimates for a comparator. This yields an incremental cost-per-QALY estimate which, compared to a threshold cost-per-QALY benchmark provides the basis for pricing discounts to achieve a hypothetical fair price for each cost-per-QALY threshold.

THE ICER/OHE WHITE PAPER

Building on what they see as a successful approach to aligning patient value and prices (fair price and fair value), ICER and OHE have moved on to consider appropriate cost-sharing and utilization management to arbitrate what they see as the inevitable tension between, in the private sector, 'providing insurance that maximizes personalized choices and the need to manage resources fairly within budget constraints'. In other words, rationing or, in less blunt terms, to 'steer patients and clinicians towards evidence-based use of treatments that achieve equal or better outcomes at lower costs'. Having established through the construction of mathematically impossible imaginary worlds the 'fair price' 'there is an equal need for consider a further policy of fair access to pharmaceuticals' with the objective of 'how to assess and judge specific cost-sharing provisions and prior authorization protocols'.

The White Paper focuses narrowly on two areas where plan sponsors and payers have direct control: cost-sharing provisions (e.g., patient co-payments) and utilization management (e,g., prior authorization). Given this focus, the White Paper addresses five domains:

- **Cost sharing provisions and tier placement as part of drug benefit design**
- **Timing of development of prior authorization protocols following FDA approval**
- **Clinical eligibility criteria**
- **Step therapy and coverage requirements to switch medications**
- **Restrictions on prescriber qualifications**

For each of these domains the White Paper 'provides a conceptual analysis of the ethical and practical tradeoffs that plan sponsors must navigate when deciding how to strike a reasonable balance between cost control and less constrained access'. ICER/OHE then present 'specific fair design criteria by which to develop and assess benefit designs and utilization management'.

Unfortunately, the balance between cost control and less constrained access rests on the myth of an I-QALY fair value price. In the case of cost-sharing provisions we are asked to imagine a situation. Consider ICER/OHE design criteria for cost sharing; the notion of an established fair value threshold (as determined by the mythical I-QALY simulation for each drug) is central to the design criteria:

- **At least one drug in every class should be covered at the lowest relevant cost-sharing level unless all drugs are priced higher than an established [mythical] fair value threshold**
- **If all drugs in a class are priced so that there is not a single drug that represents a fair value as determined through [I-QALY] value assessment, it is reasonable for payers to have all drugs on a higher cost-sharing level**
- **If all drugs in a class are priced so that they represent a [mythical] fair value, it remains reasonable for payers to use preferential formulary placement with tiered cost sharing to help achieve overall lower costs**

It is a mystery as to how these criteria are to be applied in formulary design when we have no basis for determining a fair price; presumably some I-QALY modeling will be applied to all drugs in the class with a cost-per-I-QALY threshold, all underwritten and applied by a consortium of manufacturers and the various health plans. Apparently, the proposed cost-sharing design is to be presented to patients who may be considering enrolling in the plan, together with presumably the claimed fair price. It should be explained to those patients that the cost sharing proposals for their particular health state are imaginary and can be vary depending on the methodology employed.

As a further example of the mythical fair price in formulary design, consider the question of prior authorization for access. The ICER/OHE position is that if unless a drug is considered unreasonably or unfairly prices, then access should not be constrained for coverage criteria narrower than the FDA label. Against this, if it is considered that the drug is 'unreasonably' priced. In this case resources spent above a fair clinical value (undefined) 'contribute to a net harm (undefined) in the insured population by increasing insurance premiums out of proportion to the health gained'. It is not clear whether in this case ICER/OHE is referring to some narrow concept of clinical justification or to the I-QALY fair price simulation threshold. The latter is likely as the text refers to the 'formal evaluation of the price according to transparent standards', although the imaginary I-QALY simulation is not specifically mentioned.

The first problem is that it is not clear what costs encompass? A 'fair price' claim does not translate to a 'fair cost' claim. Product 'fair price' is only one element in the cost of treatment. Are we to assume that the prices or unit costs of other medical inputs are 'fair'? If a patient is asked to share the costs of a 'far price' pharmaceutical, does this extend to co-payments for other inputs such as physician visits? Presumably, claims for outcomes achieved do not rely exclusively on the 'fair price' drug input? If a formulary is redesigned following application of the ICER/OHE criteria how are we to operationalize measures to capture any change in the non-pharmaceutical costs of treatment? Is this supposed to occur across the board for all disease states and patients covered by that health system or are these formulary redesigns intended to apply to target patient populations within a disease state? Presumably it is the latter scenario where, with a defined target population that is consistent with the FDA approved indication for a new (say) biopharmaceutical we can track drug and other medical costs before and after the formulary design change as the new product is introduced and taken up by providers and patients. This does not mean, of course, that the prior formulary design failed to meet 'fair access' criteria or that the new formulary design fails either. The absurdity of the situation is that without a 'fair access' reference, hopefully on at least and interval scale, we have no metric for change or improvement.

The second problem is the impact of the formulary design change on outcomes reported by providers and patients. If we are to judge the impact of some notion of 'benefit' then we need to be quite clear on what the benefits actually are. Attempting to apply an umbrella multiattribute measure of benefit, such as the I-QALY is clearly nonsensical for the reasons given above in rejecting the notion of a fair price. Rather we have to consider specific attributes: both clinical and quality of life. These may include both clinical markers with ratio or interval scales, as well as patient reported outcomes (PROs) that meet interval properties

for response to therapy. In other words, the instruments must conform to the axioms of fundamental measurement. At the same time we may have to consider the caregiver and the impact of formulary redesign and 'fair access' on the quality of life of the caregiver. This is a tall order as there will probably be a range of specific, dimensionally homogeneous attributes that would have to be tracked, but without any composite measure to give a 'balance' of benefit change.

The obvious fly in the ointment is the fact that the ICER/OHE reference case I-QALY modeling says nothing about a 'fair price'. Recommendations for 'fair' threshold driven pricing based on generic multiattribute preference weighted ordinal utilities are untenable; hubris becomes nemesis. What ICER and OHE fail to recognize is the need to consider benefits for target patient populations within disease states and tailor claims for benefits to potential response and resource utilization attributes that meet the standards of normal science that only accepts claims that are credible, empirically evaluable and replicable. If we cannot agree (and never will) on an unambiguous measure for a 'fair price' then notions of cost-sharing and 'fair access' collapse because there is no agreed reference point for the cost of the product and its contribution to direct medical costs. If there is no reference 'fair price' to set drug costs then we have to fall back on the 'price' of the product as determined by negotiation; to include pricing under value contracts and discounting for groups within the target population. Indeed, we have to question whether the notion of cost-sharing makes any sense where costs are a multiattribute measure of resource use.

The ICER/OHE proposed recommendations for cost-sharing and utilization management rest on the assumption that a 'fair price' for a product has been determined; absent a fair price claim and the analysis is unmoored. The cart is not only put before the horse but the horse in well on its way to the knackers yard. More to the point is the question of whether the notion of a 'fair price' has any meaning. Based on the I-QALY, it is clearly an analytical dead end. But can it be resuscitated or should it be put to one side? Does the notion of 'fair access' suffer from a similar lack of meaning? Certainly, in closed formularies in the commercial market cost sharing is typical, subject to exceptions requested by providers. Information standards and formulary decision procedures vary. Formularies may be integrated where a single committee makes a decision or separated where, once the clinical evidence has been appraised, the decision is them passed to a second committee for financing and contracting. The key question is how the information that is sought is factored into the formulary decision? Does the formulary committee consider the question of a 'fair price'? If so, are they aware of the fact that the ICER proposal for a fair price is untenable?

ESTABLISHING EVIDENCE STANDARDS

The mistake made by those who subscribe to the I-QALY myth is that there is a single 'gold standards' measure of effectiveness: quality adjusted life years. Hence we can make an imaginary claim that, in a comparative assessment, one product is cost-effective. This misses an important point: effectiveness for a therapeutic option in a target population comprises multi-unidimensional attributes; it is not a single multiattribute score such as the EQ-5D-3L. The various attributes are typically disease specific including clinical claims, quality of life and resource utilization. Effectiveness is defined as a profile of dimensionally homogeneous or unidimensional attributes. Decision makers determine which attributes are critical in evaluating response to therapy. There is no other option. This is not new and has, for example been a commonplace in multi-criteria decision analysis (MCDA). The differences here are (i) the insistence that the instruments that are capturing these selected attributes meet the standards of fundamental measurement and (ii) that there is no advantage in attempting to aggregate and weight the various attributes to create a single score. This, to press the point, is why attempts to create measures of fair value price flounder; the utility is a generic multiattribute metric encompassing attributes that may be of little, if any, relevance to patients in that disease state, not to mention caregivers.

The formulary committee is in the box seat. They have to request a submission from manufacturers; unsolicited submissions are not accepted. This allows the formulary committee to determine the evidence standards for the product. Following the recently released version 3.0 of the Minnesota proposed formulary submission guidelines the formulary committee should reject reference case imaginary worlds, impossible cost-per-I-QALY claims and the application of I-QALY thresholds to support an imaginary 'fair price' for the product. Instead, as the first step, we should focus on the target patient group within a disease stare as defined by the approved indication with the manufacturer creating a socio-economic and clinical profile. The second step is for the manufacturer to determine information or evidence gaps. What additional information is required – including clinical response, quality of life and anticipated resource utilization? Third, the manufacturer should propose what it sees as the claims that should be made for the product; to include claims for clinical response in a real world treating environment, quality of life claims and claims for resource utilization. The formulary committee should propose areas for proposed claims and the measurement standards required for the claims: all claims should focus on single attributes (dimensional homogeneity) with response consistent with the axioms of fundamental measurement. Claims, as the Minnesota guidelines detail, should be accompanied with a claims assessment protocol, identifying the evidence base proposed for evaluating the claim, the evaluation timeframe for reporting and whether or not this is a

claim that should be tracked over the patient's lifetime. The claims should be appropriate to the needs of the target population, to include not only the patient but those of caregivers.

NEGOTIATING FORMULARY ACCEPTANCE

Negotiations for pricing and product access cannot take place in an information vacuum; creating imaginary information is not a viable option. Parties to the negotiations, including third party interests such as patient advocacy groups, should recognize that initial decisions on pricing and access are provisional, subject to an ongoing review process as further evidence from claims assessments complement and potentially modify (or even reject) initial clinical claims and provisional indirect comparisons involving network meta-analyses. The key is to agree a timetable and prioritize claims assessments and reporting. This is where the evidence base, it could be a registry for a targeted sample of patients, becomes an essential part of the process. Again, the focus is on real world evidence as a dynamic process, not a static reference case imaginary world supporting 'fair prices' which might be re-run as assumptions change but where claims made fail the standards of normal science. Fantasy must not trump reality.

BUDGETS AND RATIONING

A common myth in health care is that budgets are necessarily fixed and rationing has to be introduced as a response to a presumed fixed budget in a disease area, or an aggregate budget for a health system, in order that the budget is equitably assigned. In rare diseases where we are now seeing products gaining market approval which promise a marked improvement in the quality of life of patients and caregivers, there is no reason why health system budgets should not expand. Certainly, we may judge that a price and then the associated annual costs of therapy are 'high'. This is a judgement but not one that an appeal to an imaginary 'fair price' can resolve. We do not have a framework for reconciling claims for a 'fair price' and 'fair value' and we are unlikely ever to have one. The answer is to focus on real world evidence: what evidence does a formulary committee need to negotiate what it considers a reasonable price, including value or outcomes contracts with manufacturers? If we can assure the parties that we are committed to evidence-driven value contracting, then there is increased scope for contracting to deliver the greatest possible benefits to patients who are, after all, the final consumers. Certainly this may involve cost-sharing, but not to the extent that patients are shut out from therapy.

A point that, while not glossed over, but which does not receive sufficient attention is the definition of 'cost-sharing'. Is this intended to be restricted to drug costs or is it intended to

embrace the total cost of therapy. After all, patients may be asked to meet a drug co-payment, but this also applies to other medical resources such as physician visits. A decision by a patient to meet a percentage of listed drug prices is surely not divorced from co-payment costs for medical services to support that utilization. This comes back to the old argument over silo budgeting: a drug budget versus a resource utilization budget. The extent to which a formulary might be judged to have met fair access criteria may be quite different if the focus is on the silo drug budget.

AN ADAPTIVE OUTCOMES FORMULARY

Again, negotiating for value contracts, including commitments by manufacturers to support low income patients, must be evidence based. All involve credible and evaluable claims which should be monitored and reported. Attempting, as ICER/OHE have proposed, to establish 'fair access' guidelines is a measure of our ignorance; of our limited information at product launch of the therapy benefits (if any) of a new product. Our approach to formulary decisions must be adaptive and evidence driven. If we want to this as a formulary promoting efficiency in the allocation of resources for patients in a target disease group then, by analogy to the concept of market efficiency, the efficient market hypothesis where behavior is rational and an asset's price should reflect all available information, then the evidence would suggest, at least from financial markets, that the markets are adaptive and efficiency varies over time; this variation reflecting uncertainty and the choice of relevant information [6]. Certainly the structure of pharmaceutical markets differs from the platonic perfect market ideal with asymmetric information and possibly irrational behavior. But this does not mean that there is a significant difference (whatever that means) in the efficiency of pharmaceutical markets and the notion of an efficient market. What the analogy with efficient markets points to is the need, possibly, for greater transparency in information flows, the presence of uncertainty, the ability to create and adapt to new sources of information and changes in market participation and structure (e.g., entry of new products). Formulary decisions must be part of this adaptive response.

In the Minnesota guidelines one proposal for claims assessment is to monitor the uptake, adherence to and discontinuation of therapy. Manufacturers are asked to provide evaluable claims, supported by a proposed evaluation protocol, to provide projections for the rate of product uptake, adherence to therapy and anticipated therapy discontinuation. Clearly, the design of a formulary and the costs imposed on patients for product access and the ability of patients to sustain that commitment is a key element in formulary design. We know, for example, that in many instances duration of medication adherence is fleeting with a high proportion of patients discontinuing therapy within 12 months. Proposals for formulary tiers

and drug cost-sharing should, if the formulary is outcomes focused, factor both uptake and discontinuation into the decision but also establish feedback to monitor claims for the impact of tier placement and, if part of the access design, the impact of prior authorizations.

CONCLUSIONS

If ICER/OHE believe *that payers and other stakeholders can now talk concretely (albeit without full consensus) about the conceptual framework for determining what would be the fair price for a drug*, then ICER/OHE is badly misinformed. Certainly, the market for pharmaceutical products is far from the efficient market ideal, with the presumption of a divergence between fair value and fair price. Unfortunately, attempts to bring fair price in line with fair value through the construction of fantasy I-QALY simulations and thresholds achieve nothing. Indeed, the models, thresholds and recommendations may not be 'approximate information' but approximate disinformation. The ICER (and NICE) fair price fantasy worlds are hardly a basis for going forward to notions of fair access.

There is little doubt that ICER/OHE will continue to advocate the mythical fair price approach to formulary design. ICER/OHE apparently believe that, despite all evidence to the contrary that utility scores, such as the EQ-5D-3L have ratio measurement properties. ICER believes that the I-QALY is a mathematically appropriate construct and that imaginary assumption driven lifetime simulations are decisive in formulary decisions and pricing. In this brave new world of fair pricing we can look forward to ICER/OHE consortium producing an annual fair pricing list for all approved pharmaceuticals with, by subscription, weekly updates as the assumptions of the myriad I-QALY imaginary simulations change, the models re-run and revised fair prices are issued. An enticing prospect is that the ICER/OHE fair pricing compendia will produce fair prices for a range of cost-per-I-QALY thresholds so that threshold, or willingness to pay, preferences can be accommodated. At the same time, recognizing a potential business opportunity, other modeling groups will likely emerge to produce competing simulation modeled fair price lists and weekly updates with competing thresholds.

While there is not an information or evidence vacuum, the issue that is not addressed is the specification of an evidence base which would allow us to assess, for target patient groups within disease states, the quantitative impact of formulary design changes. The notion of fair access lacks legs if we cannot quantify and track the impact on resource utilization (including drugs) and patient outcomes that meet the axioms of fundamental measurement; outcomes that are specific to the needs of the target patient population and caregivers. This requirement for an evidence base has broader implications. There are, for example, a number

of value based contracting arrangements that have protocol specific evidence requirements to support tracking and validation of initial claims. These would include financial based risk contracts, health outcomes based contracts, mortgage models, indication specific pricing and volume based pricing. The common denominator in all of these arrangements is access to data to support contractual outcomes claims. Certainly there is access to a range of data sets including administrative claims data and electronic patient records, but these are limited in respect of the ability to capture meaningful outcomes claims specific to disease and therapy areas. Data are the currency that allows us to evaluate the impact of formulary design changes. Claims for the impact of the proposed changes must be credible and empirically evaluable. Imaginary fair price claims are irrelevant and should be ignored.

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