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HAS Should Not Be NICE: Rejecting Imaginary Worlds in the French Technology Assessment Guidelines

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Abstract

Pricing decisions and access to pharmaceuticals should be evidence based. Unfortunately, the French guidelines for technology assessment, in their adoption of the National Institute for Health and Clinical Excellence (NICE) reference case modeling standard ensure that this is not the case. Rather than requiring the submission of claims that are credible, evaluable and replicable, the Haute Autorité de Sante (HAS) mandates the creation of imaginary worlds to support comparative effectiveness and cost-outcome claims. The purpose of this commentary is to make the case that HAS should reconsider this commitment to standards for health technology assessment that are more appropriately seen as pseudoscience. The recommendation is that HAS should put to one side mandating lifetime cost-per-quality adjusted life year (QALY) or life years saved claims in favor of short-term claims that can be evaluated and reported to health system decision makers as part of a provisional assessment of new products as well as supporting ongoing disease area and therapeutic class reviews.

Keywords: HAS, NICE, French guidelines, imaginary worlds, credible standards

Introduction

In an Editorial in the *European Journal of Health Economics* in 2013, the question was raised as to whether or not the National Authority for Health (HAS) should become a French version of the UK National Institute for Health and Care Excellence (NICE) in the reference case submission standards required from pharmaceutical companies [1] [2]. More recently, Massetti et al in 2015 published a detailed comparison of the HAS and NICE guidelines pointing to both their commitment to a common methodology yet emphasizing the flexibility of the HAS guidelines in contrast the mandated reference case that is central to the NICE paradigm [3]. The purpose of this commentary is to raise a question that was overlooked in both these papers: do the HAS guidelines meet the standards of normal science in a commitment to presenting competing claims for the cost-effectiveness of drug products that are credible, evaluable and replicable?

Over the past 25 years, recommendations and standards for assessing the merits of competing health care interventions have focused on informing decision makers through the construction of reference case imaginary worlds [4]. In the past nine months a number of commentaries have been published pointing to the lack of scientific merit in this approach to the economic evaluation of claims for pharmaceutical products and devices. These commentaries include reviews of technology assessment standards in the UK, Canada, Ireland, Australia, New Zealand and the Netherlands, together with the proposed European Union standards proposed under the EUnetHTA umbrella.[5] [6] [7] [8] [9] [10]. These commentaries concluded that the respective standards for economic evaluation are best seen as pseudoscience in their advocacy of quality adjusted life year (QALY) models to inform decision makers; they have more in common with intelligent design than natural selection [11] [12] [13].

Rather than a commitment to claims for competing products that can be assessed through well-designed clinical trials or systematic observational studies, the view, as stated in the draft for the latest Canadian guidelines is that: *Economic evaluations are designed to inform decisions. As such, they are distinct from conventional research activities, which are designed to test hypotheses.* Unfortunately, as pointed out on a number of occasions in previous commentaries, building simulations to 'inform decisions' is hardly an acceptable basis for formulary decision making as we have no idea whether the constructed claims are right or even whether they are wrong. Indeed, the lifetime framework advocated for the decision framework, means we will never know. The claims are immune to failure. Simulations can be engineered to generate the required cost-per-QALY claims. Setting up a reference case to mandate simulation parameters does not mean that there is not scope to create competing imaginary worlds with conflicting, yet unevaluable, be claims. One result of which is

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that when competing simulations are presented by manufacturers to formulary committees, simulated claims which more often than not as an integral part of a marketing plan support the manufacturer's product, there is no standard for judging the merits of one claim versus another other than through a comparison of the various model structures and their assumptions[14] [15] [16] [17] [18]. Discriminating through hypothesis testing is put to one side.

The HAS Guidelines

Under the 2012 law for the Financing of Social security, as described by de Pouvourville, HAS is required to consider cost-effectiveness when new drugs and devices are being assessed. HAS is then required to make recommendations for access to reimbursement together with an assessment of relative value versus comparators. Criteria employed are: relative efficacy, safety and form of administration. This establishes the relative therapeutic index (ITR) for the drug as a guide to pricing. HAS does not make final determinations. This is the responsibility of the Economic Committee for Health Projects (CEPS). A cost-effectiveness analysis is complementary to a reimbursement decision. Under the decree of October 2012 the elements that should be included in the dossier include product efficacy, quality, safety, cost, public health benefits, quality of life, access to care and ethical compliance.

The HAS guidelines are very much in line with the standards found in guidelines that follow the NICE reference case paradigm. The focus is on utilizing a decision model framework to construct an imaginary world, a reference case that utilizes either cost-utility or, where quality of life is not an important consideration, cost-effectiveness analysis. The reference case has two levels of recommendations: required and preferred. The required default timeframe is one that is long enough to reflect all expected differences in costs and health effects. In practical terms, for chronic disease, the lifetime of the modeled cohort. Required outcomes are quality adjusted life years (QALYs) for cost-utility analysis and life years in cost-effectiveness models as preferred outcomes. The required outcome criteria for the reference case are an efficiency frontier and the calculation of an incremental cost-effectiveness ratio for non-dominated interventions. The detail of the guidelines is covered in 20 recommendations that cover the type of economic evaluation, perspective, target population, comparators, time horizon, comparators, discounting, data sources, outcome measures, costs, choice of model, uncertainty and presentation of results.

As detailed by Massetti et al, there are a number of similarities between the standards mandated by HAS in the reference case and those mandated by NICE. The key similarities are in the preference for a cost-utility analysis to define the outcomes of competing interventions, the identification of subpopulations, the specification of comparators, the default lifetime horizon for decision modeling, the focus on effectiveness rather than efficacy and the application of sensitivity analysis to capture uncertainty in the decision model. The major differences are the option, if it can be justified, for cost-effectiveness analysis where outcomes are expressed in incremental costs per life year gained, defining the target population, the absence of an absolute threshold for deciding on the technology's acceptability, methods for the valuation of quality of life and the place of the recommendation in the decision process. The last point is worth noting. Under NICE the economic evaluation is seen to have a major influence in the decision as to whether or not a technology should be employed with the limited budget of the National Health Service (NHS) while in France the technology appraisals are seen as supplementing, along with budget impact assessments, pricing negotiations between the manufacturer and CEPS.

While these differences between the standards mandated by HAS and NICE are of interest, particularly in the context of the French model for pricing negotiations, the fact remains that both HAS and NICE are asking manufacturers to construct imaginary worlds. There is no requirement in either guideline that the manufacturer should produce claims that are credible, evaluable and replicable. All the health technology assessment is required to do is to 'inform' the respective decision makers. Presumably, if the reference case standards are met then, apart from the possibility that an external review group may be asked in the French case to evaluate a manufacturer's model, as required by NICE, the acceptance or otherwise of the model rests on the assessors' belief that the model has a sufficient correspondence to some 'reality'. If the correspondence is judged sufficient then, as an input to formulary and pricing decisions, the claims are necessarily accepted.

Discussion

While not explicitly stated, it is clear that it is not the purpose of the HAS guidelines for product claims to be presented that are evaluable through either hypothesis testing or systematic observation. This is quite clear from the adoption of the reference case. A lifetime or long-term perspective in modeling and the specification of an efficiency frontier with incremental cost-outcomes claims ensures that any claims made are immune to failure. Accepting this position puts to one side any notion of progress in evaluating the impact of competing health technologies in target populations. There is a complete lack of feedback on product performance to health care decision makers. Most importantly, apart from requirements to report on product safety, manufacturers can step back, agree to a negotiated price, and feel comfortable that the modeled claims can never be scrutinized.

Even if we are prepared to accept the NICE reference case paradigm, as the majority of health care systems seem prepared to do, the mandated standards are still deficient. In previous commentaries in this series it was noted that two issues appear to be ignored in the reference case standards. These are a failure to accommodate: (i) anticipated patterns of product adherence and persistence and (ii) potential future increases in the price of the product. The obvious question in respect of adherence and persistence is why, when the majority of patients discontinue their therapy within two to three years of the index prescription (and with many exhibiting a sub-clinical adherence prior to discontinuation) the reference case mandates a default lifetime perspective for the decision model? There is a substantial literature on the determinants of product discontinuation, pointing to the patient's perception of lack of effectiveness, side effects, cost and the entry of new products. Unfortunately, this is put to one side in focusing on the technical challenges of building lifetime decision models. In common with the NICE reference case the HAS model puts anticipated compliance behavior to one side.

A further issue, which has been touched upon in previous commentaries, is the currency of a simulated or modeled claim. Presenting competing claims in the framework of a lifetime reference case cost-per-QALY model raises the question of how to accommodate potential price increases for drug products and devices if the exercise is to generate claims that 'meet', for example, lifetime willingness-to-pay cost-per-QALY thresholds. In the US, for example, models developed by the Institute for Clinical and Economic Review (ICER) exclude any attempt to factor in possible long-term price increases [19]. Even if the NICE lifetime reference case paradigm is accepted by decision makers, the absence of modeling potential price increases restricts the currency of any argument that the product meets willingness-to-pay thresholds. It flies in the face of abundant evidence that, even with clams for moderation in price increases and, in the US in particular, policies to offer discounts or free access to offset co-payments, manufacturers are committed to a policy of systematic price increases over the patent life of a product [20] . These increases, semi-annual and annual, are all too often in double digits which means that within five or six years the product price, putting to one side possible discounting arrangements, is doubled. If the potential for price increases are not mandated as a reference, case standards then any efficiency frontiers and claims for incremental cost effectiveness have little relevance beyond the immediate timeframe.

Rather than focusing on the construction of imaginary worlds to justify product pricing, possible premium prices and formulary listing, the solution proposed here is to focus on short term models; models than can generate claims that are credible, evaluable and replicable, and as a result, provide feedback to decision makers in a meaningful time frame. In order to illustrate how this could be implemented, the Program in Social and Administrative Pharmacy at the University of Minnesota, has published a set of proposed guidelines for formulary committees [21]. These set standards for modeled claims, either as extrapolations from clinical trials or as stand-alone models, which can be evaluated within a two-year time frame. The key requirement is that submissions for new products should be accompanied by a protocol detailing how the claims are to be evaluated and reported to a formulary committee. It is the responsibility of the manufacturer to underwrite the study design or to report on the results of a parallel study that may have been undertaken as part of another submission. There is no restriction on the type of claim as long as it is evaluable and is acceptable to the formulary committee. The claim can be expressed in utility as well as clinical effectiveness terms. Unless the timeframe for disease survival is short (e.g., in metastatic cancer interventions) claims expressed in cost-per-QALY or cost-per-life year saved would not be considered credible. Even so, there are further questions as to the relevance of QALY measures with observed and calculated utility values varying significantly, together with concerns over preference consistency and the choice of QALY measure [22]. There are, in fact, instances of short-term models that have been published over the last few years [23] [24]. These short term models which in these instances, consider the effectiveness of biologic treatments in rheumatoid arthritis in a Spanish target population and percutaneous coronary interventions in a French target population demonstrate the ease of constructing short-term models with evaluable claims.

Redrafting The HAS Guidelines

It was pointed out in a review of the recently released version 5 of the Australian PBAC guidelines that abandoning a reference case standard does not require a complete rewriting of the guidelines. Standards required for comparative clinical claims can remain unchanged but with the proviso that their re-assessment should be an integral part of the protocol assessment. This reflects concerns expressed over the last fifteen or more years on the difficulty of reproducing phase 2 and phase 3 clinical trial claims [25]. All too often claims from a limited evidence base are taken at face value, either to support value propositions for product superiority or as input to modeled claims for cost-effectiveness. Requiring manufacturers to underwrite a claims assessment protocol would go a long way to alleviating concerns as to the veracity of clinical claims in target populations and subpopulations.

The single most important modification of the HAS guideline would be to require claims to be evaluated and, if necessary, replicated in target populations within a 2-year timeframe.

This would ensure that manufacturers presented credible claims. At the same time the guidelines could follow of Minnesota standard and require manufacturers to submit a claims assessment protocol. A commitment by a manufacturer to underwrite a protocol as a condition for their product to be reviewed for formulary listing and pricing is also important given the number of instances in which authors of national guidelines have pointed to the difficulty of populating reference models with 'national' data. The HAS guidelines are no exception. More generally, France does not possess the wealth of administrative claims and linked patient and hospital records that in found in the US and which facilitate low cost observational studies. This puts a premium on study protocols, funded by manufacturers, to evaluate both clinical and cost-effectiveness claims in French target populations to justify modeled claims and to support market entry price negotiations and prospective price increases.

Conclusions

If claims made for the comparative performance of drugs and devices are to meet the standards of normal science, then France needs to reject what has been described as the NICE paradigm and redraft the HAS guidelines. Modeled claims can still inform decision makers but in the context, not of an imaginary world with claims driven by constructed evidence, but one where there is a commitment by all parties to support a progressive research strategy. The focus of the strategy should be to report and monitor the health benefits of pharmaceuticals in target patient populations. Mandating claims evaluation can encompass not only initial product listing, where pricing and listing can be considered provisional, until manufacturers report on the outcomes of the claim evaluation, but also ongoing disease area and therapeutic class reviews. Deciding on whether or not a technology is efficient, as the basis for a pricing decision, seems pointless when the claims presented are non-evaluable. After all, in contributing to the invention of science, Descartes in the *Discourse on Method* (1637) played a seminal role in recognizing the importance of proposing explanations that could be tested experimentally [26].

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