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Abstract

Pricing by the manufacturers of the two PCSK9 inhibitors recently approved by the FDA, evolocumab and alirocumab, has led to an ongoing debate over the value of these interventions in clinical practice. In the US, the Institute for Clinical and Economic Review (ICER) has been in the forefront of those who have argued that, in the context of notional incremental willingness-to-pay thresholds, manufacturers should reduce drug prices substantially. This conclusion has been echoed in a number of other technology assessments, notably in assessments by the National Institute of Health and Care Excellence (NICE) in the UK. At the same time, other evaluations have reported favorably, arguing that at current US prices, the two products meet willingness-to-pay benchmarks. The purpose of this commentary is not to argue for or against current PCSK9 pricing policies but to point out that the case made for possible price adjustments rest upon technology assessments that fail to meet the standards of normal science. Modeled claims that are properly classified as pseudoscience. The claims made are non-evaluable. Formulary committees, rather than accepting these claims at face value, should step back and work with manufacturers to develop claims that are targeted, robust, evaluable and replicable in a timeframe where feedback on PCSK9 outcomes are meaningful to health system decision makers.

Keywords: PCSK9 inhibitors, evolocumab, alirocumab, ICER, AMCP, QALYs, cost- utility, imaginary worlds, pseudoscience

Introduction

The recent overview of the 22 commentaries on health technology assessment published in *INNOVATIONS in pharmacy* between July 2016 and February 2017 has emphasized the importance of distinguishing science from pseudoscience in published claims for product performance [1]. These commentaries have made clear that constructing imaginary worlds to support hypothetical cost-effectiveness claims for new products puts to one side any commitment to the standards of normal science; an advocacy of intelligent design rather than natural selection. Rather than supporting modeled claims or hypotheses that are credible, evaluable and replicable, model builders ask health care decision makers to take their word for claims and recommendations based on the creation of imaginary worlds. These include the reference case mandated by the National Institute for Health and Care Excellence (NICE) in the UK and, most recently, version 4.0 of the guidelines released by the Canadian Agency for Drugs and Technologies in Health (CADTH) in March 2017 [2 3]. In the latter, it was made quite explicit that the guidelines are not intended to be judged by the standards of normal science. They are intended, in setting criteria for the construction of imaginary simulations to support cost-outcomes claims, to 'inform' health system decision makers, not to test hypotheses.

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Lifetime or long-term modeled claims for comparative product performance are, by definition, immune to failure. Health care systems have no idea whether the claims are right, if they are wrong, if they are misleading or even if they should be taken seriously. This dilemma applies both to clinical claims, which are typically put forward as indirect comparisons from network meta-analyses, which should be seen as hypotheses and not taken at face value, and to cost-outcomes claims. In the latter case the exemplars are the modeled, yet unevaluable, incremental-cost-effectiveness ratio (ICER) claims and the resulting unevaluable lifetime cost-per-quality adjusted life year (QALY) claims. These unevaluable claims, together with the application of probabilistic sensitivity analyses and cost-effectiveness acceptability functions, are seen by professional associations such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Academy of Managed Care Pharmacy (AMCP) as the gold standard in constructing models to support formulary submissions [4 5]. A situation which is reinforced by the willingness of leading health technology assessment journals to publish unevaluable modeled claims [6 7 8] The downside here, for those who subscribe to the scientific method, is that there is now an accepted role for imaginary constructs in health technology assessment; a belief that non-evaluable, lifetime comparative product claims are sufficient to support formulary decisions. This is a commitment to pseudoscience (a.k.a pure bunk) [9]. This position, as emphasized in previous commentaries, flies in the face of the Royal Society motto (founded 1660; Royal Charter 1662): *nullius in verba* (take no man's word for it) [10]. The Royal society website notes that this is an 'expression of the determination of Fellows to withstand the domination of authority and to verify all statements by an appeal to facts determined by experiment' [11].

The purpose of this commentary, given the accepted standards of normal science that have been for the in place for the last 350 years, is to consider the status of the various modeled claims put forward following the marketing approval in the US for the two PCSK9 inhibitors for reducing low-density lipoprotein cholesterol (LDL-C) levels: evolucumab and alirocumab The PCSK9 models considered are: (i) the ICER evidence review model [12]; (ii) the Kazi et al revisiting of the ICER model [13]; (iii) the Arrietta et al model [14]; (iv) the Gandra et al model [15] ; (v) the Toth et al model ; (vi)[16] the Jena et al social value model [17]; and (vii) the Shah et al comparative cost of treatment model [18].

Models have also been developed in other countries, in particular the models developed by the respective manufacturers for submission to NICE, together with the models developed by the NICE evidence review group [19] [20] [21] [22]. These models are not considered in detail given the price differentials for the PCSK9 inhibitors between the UK (and European Union countries) and the US. Even so, the criticisms put forward here are relevant: none of the European models meet the standards of normal science. Although outside the scope of the present commentary, similar objections would apply to simulated incremental cost-utility claims for risk thresholds in the initiation of statin therapy in cardiovascular disease primary prevention [23].

As well as considering the merits (or lack of them) in the various PSCK9 models and their recommendations (or otherwise) for price discounting, this commentary also reviews the case for willingness-to pay cost-per-QALY thresholds in recommendations for price discounting. This is of particular interest given the standards for QALY thresholds proposed by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Performance Measures [24].

The PCSK9 Modeled Claims

It is important to recognize the limitations of the PCSK9 evidence base. Without endorsing the construction of imaginary worlds, it is all too common for researchers to rush to judgement by constructing models where the key clinical inputs are limited to a few phase 2 and 3 trials, few (if any) of which would have been replicated in treatment practice. While the Food and Drug Administration (FDA) may be prepared to grant marketing approval on a limited evidence base, health care systems are, presumably, more concerned with replicated claims for effectiveness in treatment practice. As a result, the various PCSK9 models, given their time horizon, are forced to make assumptions to support lifetime or long-term claims for cardiovascular events between the statin standard of care and the introduction of PCSK9 intravenous therapy as an add-on to the statin standard of therapy; claimed model outcomes which will never be evaluated.

A recent systematic review of PCSK9 inhibitors points to the evidence gaps [25]. The review considered results for 17 trials reported in 19 publications. Studies were graded on their limitations, directness, consistency and precision of the body of evidence: high strength, moderate strength, low strength or insufficient. The review found low to high-strength evidence of moderate to large magnitude reductions in LDC-L when added to statin therapy in patients with familial forms of hypercholesterolemia and alone or added to ezetimibe in those intolerant of statins. Although there were no head-to-head studies, the lipid outcomes were fairly similar across trials, with evidence varying by target population and drug. However, the principal concern in the review was with the lack of evidence for long-term health outcomes. The authors concluded that the evidence is insufficient to draw conclusions because of the limited or absence of information on the long-term impact of large reductions in LDL-C. More to the point, perhaps, is the fact that the studies reviewed reported cardiovascular events as secondary outcomes; the studies were not powered to assess cardiovascular events.

The ICER Model

In November 2015, ICER released its final evidence report on the PCSK9 inhibitors for the treatment of high cholesterol [12]. The goal of the report was to consider key issues that patients, providers, and payers face when making decisions about PCSK9 inhibitor therapy, in particular to assess the comparative clinical effectiveness and comparative value of the two PCSK9 inhibitors as a class for patients with elevated LDL-C. The incremental costs per outcomes achieved for the PCSK9 inhibitors were evaluated using the CVD Policy Model of cardiovascular disease in the adult (over 35 years) US population. This is a simulated, discrete-state Markov model of coronary heart disease and stroke incidence, prevalence, mortality and costs. The model cycle is 12 months. The chronic cardiovascular disease categories are: coronary heart disease only, stroke only and combined prior coronary heart disease and prior stroke. Each state and event has an annual cost and quality of life adjustment, an annual probability of an event and/or transition to another state.

ICER modeled the entire population of the US aged 35 to 74 years in the year 2015. All direct and induced medical costs and relevant clinical outcomes were modeled over this time horizon until patients reached 95 years of age. Utilities and costs were assigned to each clinical event in the annual cycle and discounted at 3% annually. Deterministic and scenario-based sensitivity analyses were applied to capture input parameter uncertainty. Three target populations were considered: (i) familial hypercholesterolemia; (ii) pre-existing cardiovascular disease but unable to tolerate statins; and (iii) pre-existing cardiovascular disease despite receiving maximum tolerated statin therapy. Treatment strategies compared: (i) ezetimbe vs. PSK9 inhibitors for statin intolerant; and (ii) statin vs. ezetimbe vs. PSK9 inhibitors as base-case (ICER Table 9). The utilities in

the ICER model were derived from the Global Burden of Disease (GBD) disability weights study. Estimated utilities ranged from no history of cardiovascular disease (utility = 1) to history of MI and stroke (utility = 0.852).

Outcomes were expressed as QALYs and ICERs in terms of both the PCSK9 inhibitors and ezetimibe relative to those tolerant/non-tolerant of statin therapy. The ICERs were calculated in terms of next most effective therapy. A willingness-to-pay threshold of $100,000 per QALY was assumed. The baseline model identified 605,000 patients with familial hypercholesterolemia which equated with 13.3 million years of treatment over 20 years. The risk of a major adverse cardiovascular event (MACE) in this population was estimated 2.2 to 3.4 times higher than an age and gender-matched population without familial hypercholesterolemia. Compared to the control arm, treatment with ezetimibe was projected over the lifetime analytic horizon to avert 115,900 MACE and produce 250,000 additional QALYs. Adding a PCSK9 inhibitor would avert 324,200 MACE and yield 665,200 QALYs with an ICER of $230,000/QALY. This was driven by differences in drug costs between PCSK9 inhibitors ($14,350 per annum) vs. ezetimibe ($2,828 per annum). Weighted by the size of the three major subpopulations threshold prices at which the PCSK9 inhibitors were projected by ICER to be cost-effective were $3,166 ($50,000 threshold), $5,404 ($100,000 threshold) and $7,735 ($150,000 threshold).

The Kazi Model

The Kazi et al model follows the Markov structure of the ICER model (there is a shared authorship) [13]. The model structure is again based on the CVD Policy Model of coronary heart disease and stroke incidence, mortality and costs for the population 35 years or older. The model included the population to 74 years of age following them over the lifetime until death or survival to age 95 years. Two base case simulations were modeled: (i) heterozygous familial hypercholesterolemia with either a family history or no family history of premature coronary heart disease and (ii) preexisting atherosclerotic cardiovascular disease. The model included estimated direct medical costs, utilities were again from the Global Burden of Disease study, assigned to each clinical event in annual cycles and discounted at 3% per annum. Three treatment strategies were considered: (i) statin status quo; (ii) incremental ezetimibe; and (iii) incremental PCSK9 inhibitors. Costs of PSCK9 inhibitors were for 2015 calculated as the mean of $14,600 for alirocumab and $14,100 for evolocumab.

The addition of ezetimibe to statin therapy was estimated to avert 214,400 MACE and 628,500 additional QALYs. Treating the entire familial hypercholesterolemia population aged 35 to 74 years (taking statins or statin intolerant) with PCSK9 inhibitors was estimated to cost $323 billion more than treating with ezetimibe but with an offset of $17 billion for reduced cardiovascular care. The net result was an estimated $582,000 per life year saved or $503,000 per QALY (vs. ezetimibe plus statin). The ICER of PCSK9 inhibitor to relative to status quo was $352,000 per QALY. At a $100,000 threshold, PCSK9 inhibitor prices would need to be $4,536 or less to be considered cost-effective.

The Arrieta Model

The Arrieta et al model considers the cost-effectiveness of PCSK9 inhibitors, again comparing a statin plus PCSK9 inhibitor against statin standard-only therapy [14]. Two perspectives were considered: (i) a health system perspective expressed as cost per QALY gained over standard therapy and (ii) a private payer perspective defined as return-on-investment and net present value over a patient lifespan. The question addressed was whether PCSK9 inhibitors add a positive net benefit to the health system and private payers.

A Markov lifetime model was proposed that followed a hypothetical cohort of patients beginning at age 58 until death or age 100 years. Model parameters were cardiovascular event, mortality, treatment costs and health utility states. Baseline characteristics mimiced those of the evolocumab trial population. The key parameter in the model was the annual probability of a cardiovascular event over the lifetime of a patient. Projected annual probabilities for age 58 and beyond were estimated by applying one-year evolocumab relative risk reduction data under the assumption that the Framingham survival function is proportional to the unobserved evolocumab survival function; the relative risk reduction was estimated at 49.2%. The model assumed a one-year cycle with patients transitioning between living a normal life under lipid lowering treatment or experiencing a cardiovascular event. After the event patients moved to a post-cardiovascular event stage characterized by a slow transition back to a normal life defined by quality of life and costs. Patients could remain in this state for up to five years, they could have a subsequent cardiovascular event or experience a cardiovascular related death. They could die of a non-cardiovascular event at any time. All costs and outcomes were discounted by 3% per annum.

The cost-effectiveness analysis took a health system perspective with the ICER defined as the difference between the differences in therapy pathway costs less any avoided costs from cardiovascular events divided by difference in QALYs sourced from the EQ-5D index score for chronic conditions in the US. These were estimated at 0.79 at treatment and for the 5 years post-event were assumed to be from a low of the 25% base score progressing non-linearly to the at treatment score. The payer perspective analysis was expressed in net present value terms as the avoided costs from treatment plus the insurance premium less the costs of treatment at a discount rate of 3% (i.e., the net present value divided by the cost of treatment). The model assumed a 12% annual turnover of plan membership.

At a PCSK9 price point of $14,000 per annum treatment costs were estimated to be $237,718 from a health system perspective and $73,137 from a payer perspective. Avoided costs due to reduced cardiovascular events were $5,800 from a health system perspective and $1,095 from a payer perspective. Cost per QALY was estimated to be $348,807. Life years gained was 0.88 and QALYs gained 0.66. Assuming a willingness to pay threshold of $100,000 per QALY, the PCSK9 inhibitoe would be cost-effective at annual cost of $4,250. At an annual cost of $14,000, PCSK9s are not financially viable for the private payer. The PCSK9s are only financially viable at a price of $600.

The Gandra Model

The Gandra et al lifetime Markov state-transition model focused on the cost-effectiveness of evolucumab added to the standard of care versus the standard of care alone in three populations with trial data available [15]. These are: (i) patients with heterozygous familial hypercholesterolemia; (ii) patients with atherosclerotic cardiovascular disease, defined as ≥ 1 prior CVD event, without statin intolerance; and (iii) patients with atherosclerotic cardiovascular disease and statin intolerance.

Health states in the model included no cardiovascular disease, established cardiovascular disease, acute coronary syndrome, post-acute coronary syndrome, ischemic stroke, post-ischemic stroke, heart failure, post hearty failure, coronary heart disease death, ischemic stroke death and von cardiovascular death. Patents could enter the model at no cardiovascular disease or at dedicated prior cardiovascular health states. Combined health states retained memory of prior events in the model. The predicted efficacy of evolocumab on reducing cardiovascular events were derived from the relative LDC-L reductions to week 12 of the clinical program. Utilities for the no cardiovascular disease health states were estimated at 0.824 for the population ≥ 45 years of age with utilities for other health states from a prior time trade-off study with 1 year evaluation of acute states and 10-year for chronic states. The WAC cost of evolocumab was $14,139. Discounts were not considered.

The incremental costs of evolocumab added to standard of care alone in patients with heterozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease without statin intolerance and patients with atherosclerotic cardiovascular disease and statin intolerance were $153,289, $158,307 and $136, 903 respectively for QALY gains of 2.02, 1.12 and 1.36. These estimates yielded cost per QALY gained estimates of, again respectively, $75,863, $141,699 and $100, 309. All ICERs met ACC/AHA intermediate value and WHO cost-effectiveness thresholds.

The Toth Model

The Toth et al model extended the Gandra et al model to estimate real-world cardiovascular disease burden and value-based price range of evolocumab in a US-context high-risk-secondary prevention population [16]. With the burden of cardiovascular disease evaluated from the UK Clinical Practice Research Datalink (CPRD), patients on high intensity statins were selected based on the FOURIER model eligibility criteria. Following the Gandra et al Markov state-transition model evolocumab plus the standard of care was compared to standard of care alone. Four treatment cohorts were considered: (i) high-risk prevalent atherosclerotic cardiovascular disease cohort; (ii) acute coronary syndrome cohort; (iii) ischemic stroke cohort; and (iv) heart failure cohort. Using the current annual cost of evolocumab (list price $14,100), the incremental lifetime costs of adding evolocumab were $127,088 for patients with a baseline LDL-C ≥ 70mg/dL and $110,916 among those with a baseline LDL-C ≥ 100mg/dL. The respective QALYs gained lifetime were 0.68 and 0.95 respectively. The respective ICERs were $190,440 and $118,905. Under the deterministic variant of the model the value-based price of evolocumab was estimated to be $9,051 for $100,000 per QALY, $11,935 for $150,000 per QALY and $14,819 for $200,000 per QALY.

The Jena Model

The Jena et al simulation model utilized projections of the population of the highest risk statin benefit groups (SBGs) with established atherosclerotic cardiovascular disease (SNG 1), LDL-C levels ≥ 190mg/dL (SBG 2) and diabetes (SBG 3) to estimate the economic value of reducing the hyperlipidemia burden among those not achieving conventional LDL-C goals by 50% through introducing PCSK9 inhibitors [17]. The economic value of averting CVD related death and MACE was estimated, first, by estimating the number of life-years gained from (i) averting a single death from clinical trial follow-up data and, because this might be an overstatement, (ii) life-years lost from ischemic heart disease from the US Burden of Disease Study and, second, from the value of reducing cardiovascular related hospitalizations. The value of life years gained and the savings from reduced hospitalizations were aggregated to generate an estimate of the value of reducing LDL-C by 50% and the value of PCSK9 inhibitors under each of the three uptake scenarios.

Value-per-person-year for those in SBGs 1 and 2 were presented for five year intervals from 2015 to 2035. Key variables were (i) number of MACE and cardiovascular events avoided in each year; (ii) value from these averted events; and (iii) value per person per year comprising cost offsets and life years to give total social value. Two efficiency scenarios were considered: an LDL-C reduction by 59% in the conservative efficiency scenario with associated reductions in MACEs and cardiovascular deaths, and a 50% reduction in MACEs in the high efficiency scenario.

The modeled estimates of net social value presented (benefits in excess of costs) suggested that this would be delivered by the PSCK9 inhibitors (at prices of $14,100 and $14,600 per year for evolocumab and alirocumab respectively) for average patients in SBGs 1 and 2 as long as the annual price was below $18,000

in a high efficiency scenario or $12,000 in a conservative efficiency scenario. As these estimates did not include any benefits from improvement in quality of life, the authors cautioned that they might be conservative.

The Shah Model

The Shah et al study tracked 103 patients on either alirocumab or evolocumab of whom 61 had a first cardiovascular event with total attributable costs of $8,904,361 [18]. The median 10 year risk of another event was calculated to be 13.1% with a total cost of $1,654,758. Assuming a 50% reduction in cardiovascular events on PCSK9 inhibitors in the 61 patients, $4,452,180 would have been saved in the past and future 10 year savings would have been $1,123,345. Net costs per patient per year were with PCSK9 inhibitors were estimated at $7,000 in the past and $12,459 in the future. The claim is that over a 10-year period the net cost of PCSK9 intervention is well below the $50,000 per year of life saved threshold.

Accepting the PCSK9 Model Claims

Apart from the fact that none of the models considered generated evaluable claims for the cost-effectiveness of PCSK9 inhibitors, the recommendations for discounts required to meet willingness-to-pay thresholds showed considerable variation. At a threshold of $100,000, the ICER et al and Kazi model et al yielded simulated cost-effective annual prices of $5,404 and $4,536 respectively with the Arrieta et al model recommending a price of $4,250 as a maximum [12 13 14]. Against these results the Gandra et al model concluded there was no need for price adjustments for evolocumab given ACC/AHA intermediate willingness to pay and WHO cost-effectiveness thresholds while the Toth et al model variant yielded a price of $9,051 [15 16]. The Jena et al lipid control model, focusing on social value, concluded that discounting was unlikely once quality of life as a benefit entered the calculus [17].

Obviously, differences in the specification of target populations for PSCK9 inhibitor therapy will impact model clams and go at least some way to reconciling differences between imaginary cost, QALY and ICER claims. In the case of the Gandra et al model, for example, the authors pointed out: (i) that the ICER model, in using the policy model, underestimated the impact of single risk-factor interventions; (ii) the underlying policy model was intended to model the entire US population not controlled on statins and not high-risk populations; (iii) the policy model underestimated the incidence of chronic heart disease by 50%; and (iv) that the ICER model does not account for the elevated risk of cardiovascular events among heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease patients [15]. Similar comparisons could be made against other models.

Beyond such differences are those attributable to the structure of the Markov model, the treatment pathway assumptions, the assumed acute and chronic disease states, modeled transition probabilities, direct medical cost assumptions and the choice of utility measure. Other potential confounding factors could include, as noted in a recent review of the ICER report on targeted immune modulators (TIMs) in rheumatoid arthritis, the extent to which relevant comorbidities and their impact on model outcomes were accommodated, the treatment of adherence and persistence (or its absence), potential or anticipated price increases for the PCSK9 inhibitors and other resources captured in the model, and possible intervention of new therapies [26].

It is, of course, always possible to compare the structure and assumptions of one modeled imaginary world against competitors, with the implicit claim that one model should be in the pole position for 'belief in' by a formulary committee. This has, it should be emphasized, nothing to do with uncertainty in input assumptions and probabilistic scenarios for cost-effectiveness. It reflects, quite simply, a belief by the model builders that if there is a sufficient correspondence to their assumptions and descriptions of perceived 'future reality' then their claims necessarily follow as 'pertinent information' for decision makers [27].

In addition, there is no reason why health care systems should adopt incremental cost-per-QALY thresholds as a decision metric or pay any attention to the construction of imaginary worlds to drive recommendations for price discounting. Certainly, in a fixed budget environment, the case can be made for incremental assessments on efficiency grounds, but it would also make sense for a health system to adopt a notional metric of a cost per life-year or a cost per QALY independent of efficiency considerations. Manufacturers would then present a case for a new 'breakthrough' therapy such as the PCSK9 inhibitors in terms of costs per life year. If for example, it could be demonstrated for a target population, over say a two-year timeframe, that the cost-per-life year was lower than a notional threshold, the product would be considered for formulary listing. Products would be considered on its clinical merits and cost implications. This would set the stage for price negotiations given the health systems' own 'value' metric. The case for a new product would be considered on its merits not as a comparative incremental benefit over therapies that may be generically priced as shown in the Jena and Shah models.

While the PCSK9 inhibitor models may have a technical appeal as an exercise in constructing imaginary treatment scenarios, the fact remains that none of them generate evaluable claims. They are, although suggestive of possible protocols to drive evaluable claims, still imaginary worlds. If we accept the standards of normal science, we should put this constructed evidence to one side, focusing instead on models and protocols that provide the basis for assessing claims in the short term. Certainly, we can take on board suggestions that more focused treatment strategies in identifying target populations may move us away from blanket statements that there need to be

substantial price discounts to justify PCSK9 market support. It is then up to manufacturers to propose how prices or price discounts from wholesale acquisition cost (WAC) may be justified in the context of evaluable claims. Evaluable claims that might be expressed in terms of willingness-to-pay thresholds or more simply in costs per cardiovascular event avoided without reference to quality of life.

Even so, there may be concerns by health decision makers that accepting 'indicative' modeled yet unevaluable claims that meet threshold criteria in targeted high-risk or other populations, may open the door to a wider utilization. Once accepted on formulary, there is no assurance that manufacturers would not pursue a marketing or Trojan horse pricing strategy that encouraged physicians to prescribe outside of the target group. It is, of course, possible that prescribing could be ring-fenced by a prior authorization requirement or health systems could attempt to monitor prescribing behavior. Manufacturers might even agree to restrict advertising and physician communications to the target population, agreeing to reimburse patients for co-payments and health systems for outlays 'off-target'. The conclusion must be that even if a targeted model meets notional outcomes standards, it should still be rejected in the absence of any evaluable and replicable claims.

This brief review has shown that where the 'gold standard' for claims rests on the construction of lifetime imaginary worlds to support PCK9 inhibitors, model builders have considerable latitude in devising their cost-effectiveness case. Options abound in the choice of target populations, model structure, selection and specification of treatment pathways, choice of parameter values (and their distributions in probabilistic scenarios), choice of resource units and their costs, selection of utilities from the range of instruments, application of algorithms for cross-walking items to utility scores and the choice of model outcomes.

At the same time, there is always the temptation to construct a 'favorable' imaginary world to support previously established post-formulary acceptance pricing strategies. After all, it is commonly observed that manufacturers often engage in long-term annualized price increase strategies so that a 'market entry' price may be little resemblance to future prices and threshold claims. The modeled 'market entry' price for the imaginary simulation may, indeed, be established simply to ensure formulary acceptance by meeting notional cost-per-QALY thresholds. As noted, none of the PCSK9 models considered here have taken into account possible future price increases. This flexibility in pricing assumptions may be a factor in the continued support for the construction of imaginary worlds in order to gain formulary acceptance.

Mandating a reference case, as health technology assessment agencies attempt to do, does little to resolve questions of the discretion and direction of model builders. Given NICE as the example, the last 18 years have demonstrated how often evidence review groups engaged by NICE to review manufacturer's submissions disagree with submitted model structures and assumptions and go so far as to put in place alternative models (which are then subject to further critique by NICE and challenges from the manufacturer). Unless there is a way of subjecting model claims to an independent check this proliferation of conflicting claims will continue. The check suggested here is to put unevaluable claims to one side and focus of claims that are evaluable, replicable and capable of providing feedback to decision makers in a meaningful timeframe.

Choose Your QALY!

The choice of a QALY measure in cost-utility models has obvious implications for cost-per-QALY claims. Different instruments yield different utility values to be applied, for example, to the various Markov stages through which a hypothetical population progresses. This is demonstrated in the models considered above where there is no standard for the choice of QALY or any suggestion as to how QALY claims in one model may be reconciled to claims made by another. Absent a common QALY measure or an agreed algorithm for cross-walking QALYs, the models are non-comparable in the outcomes claimed and, by extension, any claims for price discounting to meet cost-per-QALY thresholds. The observation that in certain models the recommendations for discounting appear to reinforce each other is immaterial; if not a red herring. In the absence of evaluable and, for example, comparable cost-per-QALY claims, no conclusions can be drawn.

Given the range of possible utility measures and the practical obstacles to reporting on QALYs in treatment practice it is of interest to consider the position of the ACC/AHA task force in recommending QALYs as a key outcome that should be captured to support transparency in value claims. The task force recognized that no national consensus has emerged in the US regarding cost-effectiveness, yet the task force hoped that the recommended performance standards would be captured by study designs incorporating resource utilization and cost benefit. The task force also recognized that QALYs may be difficult to measure and may be considered controversial in economic evaluations. Even so, although not endorsing a particular QALY measure or the methodology to capture QALYs, they were still seen as representing the preferred metric. Unfortunately, sidestepping controversies regarding the choice of QALY is difficult to square with their advocacy of willingness-to-pay thresholds with an indicated range of from $50,000 to $150,000 in value recommendations where modeled claims for value may embody different measures. To evaluate the quality of cost-effectiveness models the force report also points to the Quality of Health Economic Studies (QHES) checklist for the assessment of a cost-effectiveness studies [28]. Unfortunately,

the checklist does not address the issue of evaluable cost-effectiveness claims and their replication.

Target Populations, Modeling and Precision Medicine

Previous commentaries in this series have pointed to the potential impact of precision medicine, specifically next generation sequencing (NGS), on therapy choice, the design of RCTs and establishing evaluable claims [29] [30]. In the case of the PCSK9 inhibitors, as an example, a prior assay evaluation could indicate which members of a target population defined on empiric grounds are likely to respond to the therapy. The assay may suggest that an individual is a probable non-responder and that alternative therapies may be more appropriate; even to the extent of suggesting alternative therapies to those who are probable non-responders to the indicated therapy. If an NGS 'filter' is introduced to guide therapy choices then building imaginary claims from empiric randomized trials becomes redundant – if not potentially misleading. Rather, health systems could require, given the anticipated opportunity costs of a mismatching of patients to therapy choice, that an NGS assay be integrated as part of treatment guidelines to improve the profile of patient outcomes and quality of life. This approach may also provide a more robust basis for pricing and discounting of the proposed 'breakthrough' therapy.

Conclusions: A Rush to Judgement

Constructing imaginary worlds to support product claims and formulary decisions represent an easy way out for those involved in health technology assessment. Rather than attempting to develop and assess evaluable claims, time and resources are spent in justifying the relevance of competing constructed imaginary worlds to support and publish comparative product claims. The result is that decision makers are faced with competing modeled claims justified in terms of the reasonableness or otherwise of the model structure and assumptions. There is no way of distinguishing the various claims in empirical terms. Quite reasonably: why should decision makes pay attention to imaginary recommendations for formulary acceptance and pricing based upon constructed claims that are immune to failure?

It is understandable and, indeed even laudable, that research groups should attempt to present evidence and recommendations to support formulary decisions and pricing policies as soon as products receive marketing approval in their target indication. This does not condone, however, the creation of modeled or simulated imaginary worlds to support non-evaluable claims and, in this case of PCSK9 inhibitors, constructed recommendations for price discounts. Previous commentaries in this series have argued that, rather than constructing evidence, manufacturers should commit to underwriting protocols to support evaluable and replicable claims. These should be based upon short-term models, or based entirely on key randomized clinical trials. Formulary committees should establish guidelines to support protocols and the reporting of outcomes in a meaningful time frame to decision makers, physicians and patients. This position has been detailed in the Minnesota proposed guidelines for formulary submissions (2nd Ed. December 2016) [31]

Unfortunately, there is a long way to go before these standards for claims assessment become accepted practice in health systems. Rather, technology assessment groups and professional groups, such as the AMCP and ISPOR, are committed to the construction of imaginary worlds. This lack of correspondence to accepted standards in normal science has been detailed in previous commentaries. The result is that there are all too often, as in the case of the PSCK9 inhibitors, a number of models jostling for the attention of health system decision makers. This presents formulary committees with the task of selecting between imaginary modeled claims to justify product placement and pricing decisions. Whether this decision could be made more transparent by model builders jockeying for pole position in the modeling stakes is a moot point and, as noted in the arguments put forward here, actually irrelevant. There seems little mileage in allowing formulary committees access to simulation models when all they would be able to do would be to crank out more scenario-driven unevaluable claims.

The conclusion is that constructing imaginary worlds and unevaluable claims is, at least from the perspective or normal science, a pointless exercise. This does not mean that groups such as ICER should not continue to construct lifetime cost-per-QALY claims and make recommendations for price discounting. After all, if health technology assessment agencies globally are prepared to accept unevaluable modeled lifetime claims based on a limited evidence base, where there has been a rush to judge the pricing strategies of manufacturers, then formulary committees in the US could endorse and make clear that they subscribe to standards in guidelines such as those put forward by the AMCP. Whether these models would be taken seriously by other health care decision makers is an open question; a decision that is made more problematic when it is pointed out that there are competing models making disparate claims.

Needless to say, it is all too easy to point out that a model can be challenged and, indeed, that it is quite possible to construct alternative scenarios that could be reverse engineered to give entirely different outcomes. If we subscribe to untenable standards put in place by technology assessment agencies and professional groups, one result is that there is now a generation of researchers and graduate students who have been taught how to model imaginary worlds to generate unevaluable claims; meeting relativist standards rather than the standards of normal science and adding to the thousands of already published yet unevaluable modeled claims in health technology assessment.

Evidence and recommendations for product placement and pricing should be credible, evaluable and replicable. This is not the case where these claims are based on the creation of imaginary worlds, irrespective of whether or not they are seen by the model builder as a sufficient representation of a 'future reality'. While this may be defended on the grounds that there is no option when the evidence base at product launch is limited and it has to be 'constructed', the downside is that it is all too easy also to construct alternative imaginary scenarios to justify (or otherwise) non-evaluable claims for comparative cost-effectiveness, budget impact and product pricing that fall below (or above) arbitrary willingness-to-pay thresholds. In the absence of evaluable and replicable claims, where the model captures unknown knowns, known unknowns or unknown unknowns, decision makers are asked to take at face value recommendations for product placement and pricing. Perhaps we should close the wardrobe door on Narnia and focus on developing short-term evaluable and replicable claims for cost-effectiveness to support pricing recommendations for PCSK9 inhibitors [32].

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