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EXTENDED NONSENSE FROM ICER: CHANGING ASSUMPTIONS FOR TAKHZYRO AND CI INHIBITORS

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ABSTRACT

The Institute for Clinical and Economic Review (ICER) prides itself on the development of imaginary assumption driven simulations to invent evidence and recommendations for pricing and access. According to ICER, the opportunity should not be missed to change assumptions and recommendations once real world data become available. This enables ICER, with no embarrassment, to revisit previous imaginary claims with a new set of imaginary claims some years after the first set of recommendations have been factored into formulary decisions. The purpose of this brief commentary is to make the point that one can change any number of assumptions in the ICER analytical framework; it does not change the fact that the ICER modeling is pseudoscience and that any claims made should be rejected out of hand. The ICER modelling is just a placeholder for any number of assumption driven future placeholders driven by changing assumptions.

INTRODUCTION

Access to real world data to modify assumptions is irrelevant if the analytical framework is deficient. The ICER reference case framework, which involves creating an assumption driven simulation model to support cost-per-incremental quality adjusted life year (QALY) claims for threshold pricing recommendations, is considered an analytical dead end [1]. It fails the standards of normal science as claims lack credibility and are impossible, by design, to empirically evaluate. This places ICER clearly in the Dover courtroom, alongside intelligent design. Any assumption driven imaginary simulation can be modified by changing assumptions, in this case the frequency of acute attacks in hereditary angioedema [2] . Next time it might be a revision of the ordinal preferences for the QALY with a switch from the EQ-5D-3L preferences to the EQ-5D-5L preferences. The recently released ICER report on changing assumptions in the imaginary model simulation for prophylaxis of hereditary angioedema is in this tradition. Every ICER model and its imaginary claims is just a placeholder for a potential endless success of future models with each of these a placeholder for future models. Presumably, the intent is for a succession of provisional placeholder

modelled claims across a multiplicity of disease areas with the landscape continually in flux as new claims emerge, as a phoenix, from the ashes of the old.

INVENTIING EVIDENCE

A tradition that is now, after 30 years, well entrenched in health technology assessment is to reject hypothesis testing and the discovery of new facts in favor of inventing approximate evidence [3]. Its genesis lies in the late 1980s and early 1990s where is was concluded that rather than wait upon more data before any conclusions as to the cost-effectiveness of a new product could be considered, it was more appropriate, given limited data at product launch, to invent evidence to fill data gaps with assumption driven lifetime models to support cost-effectiveness claims [4] . While this denies the standards of normal science, with particular reference to the axioms of fundamental measurement, it was embraced enthusiastically by those who should know better, but did not. In this respect, ignorance of the standards that apply in the physical sciences was an added plus as models could be built, consulting fees earned, and claims made that could never be empirically assessed. Few models were ever re-visited with the impression that they were just marketing devices to support formulary approval.

The ICER business model rests upon a belief in evidence created by a nonsensical reference case modeling framework. ICER is in the box seat because its claims can never be countered except by new modelled claims. All a reviewer can do is challenge assumptions for the model structure and its data points. This is a particularly fruitless activity as any number of competing models could be created and even reverse engineered to create competing pricing recommendations for any number of treatment regimens.

MEASURING THE IMPOSSIBLE

ICER not only embraces pseudoscience in denying the relevance of empirically evaluable claims, but presents the claims through the creation of QALYs that are mathematically impossible as they rest on ordinal preferences [5]. ICER denies this. Instead, in defiance of the axioms of fundamental measurement, ICER insists (indeed demands an uncritical belief) that the multiattribute preference scores that are required for the QALY are indeed ratio scores and not, as has been shown on multiple occasions, ordinal scores. ICER has, in fact, made a major contribution to measurement theory in its belief (no proof) that the EQ-5D-3L ordinal scale is, in fact, a ratio scale in disguise. This is palpable nonsense. In fact, the latest US valuation of the EQ-5D-5L yields 20% of 3,125 health states with negative values or states worse than death[6] . In a disease such as hereditary angioedema, there is a strong probability

that revisiting the preference score would involve negative values. Although ICER has, presumably, no intention of doing this, it must cast doubt on the application of EQ-5D-3L preferences in the cost-per-QALY claims. Again, if we change the preference assumptions what is the impact on the imaginary ICER claims? Will ICER undertake another, possibly one of many, revisions?

DENIAL OR APPROVAL OF CARE

Should ICER recommendations be taken seriously by health system decision makers or insurers? ICER tries to protect its modeled assumptions by simple sensitivity analysis and the acme of imaginary modelling, probabilistic sensitivity analysis. If the first model incarnation is only a placeholder then changing assumptions will modify these claims, involving a revised sensitivity analysis. This is an absurd situation as a qualified series of recommendations are worthless if changing assumptions change, inevitably, the claims. It also points to the absurdity of the much publicized ICER health benefit price benchmark (HBPB). This contribution to the intellectual tool box of applied social science and welfare economics is according to ICER the highest price a manufacturer should charge for a treatment based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance; subject, of course, to the assumptions made to create this social price. On this scenario, the global all-product centrally-planned HBPB field is continually in flux with data-point decisions for resource allocation between treatment regimens and disease areas continually being revised as the imaginary HBPB data points for the field change.

The devil, as always, is in the details. In this case the series of unjustified (i.e., patently false) assumptions made in ICER's denial of the standards of normal science and measurement theory which makes clear that the QALY is mathematically impossible and the ICER analysis an analytical dead end. But ICER must have their day in the sun! Fortunately this is over; exemplified by the impact of changing assumptions. If assumptions regarding the frequency of acute attacks in hereditary angioedema can be modified once, then they can, logically, be changed again. ICER, as detailed in previous commentaries, makes the logical error of assuming in the first imaginary model that previous claims can support claims on the future. ICER has demonstrated that this is logical nonsense; the problem of induction (Hume's problem) has, once again, been vindicated: it cannot be established by logical argument, since from the fact that all past futures have resembled past pasts it does not follow that all future futures will resemble future pasts [7].

If the imaginary HBPB is taken, by those followers of ICER, as the critical element in denying access to care through the application of threshold cost-per-QALY imaginary numbers, then if the revised assumptions, as in the case Takhzyro and CI Inhibitors, increase recommendations for price discounting and raise access to care barriers, then health systems will have to consider reducing access to care or refusing it to new patients who would previously have been below the threshold. Conversely, if the HBPB is increased if the modeling previously underestimated therapy benefits and the consequent imaginary QALY claims, those previously denied (apart from the deceased) will now be admitted. Unfortunately, this relief cannot be applied retrospectively.

We don't have to wait, of course for five years, for ICER to reformulate its model and claims and shoot itself in the foot. We have the ideal opportunity through the recently developed ICER cloud based software platform, ICERAnalytics, to modify assumptions [8]. For a small fee, giving access to the ICERAnalytics platform for the models available, the possibly interested user can change any number of assumptions and produce any number of conflicting claims. ICER, as it were, is hoisted by its own petard. The global ICER HBPB field is now having to accommodate independent re-assessments of therapy claims to add to the general flux of competing claims; that way madness lies.

EUGENICS AND THE HBPB

While implicit is the previous discussion, it is worth emphasizing the role ICER plays in what might be described as a modern eugenics policy [9]. With the impossible QALY preference weights determined by the community, the QALY should be seen as a community health care allocation tool to deny and approve access to care; a tool, unfortunately, that is driven by assumption and subject to unforeseen changes as the assumptions driving the ICER model change. Nevertheless, in concert with the pseudoscience of the eugenics proposals of the late 19th and early 20th , the pseudoscience of the ICER modelling gives health systems an excuse to deny care.

The situation becomes even more absurd if analysts focus on not the EQ-5D-3L but the EQ-5D-5L to create competing ordinal scores and consequently a different class of imaginary QALYs in Takhzyro and CI Inhibitor clinical trials or observational studies. The two scores are not compatible and, as they are ordinal, crosswalking is mathematical nonsense. The revised model will then support 'new' cost-per-QALY claims in addition to revised clinical outcome claims; a reassessment process that will continue indefinitely or at least until new products enter the treatment space or patents expire.

There is the additional fly (one among many) in the ICER ointment: the creation of health states worse than death. Does, ICER propose as its future contribution to denial of care the creation of an algorithm for clinician use that would allow health systems to deny care? There is ample scope as the US preference weights, as noted, yield 20% of health states as worse than death. Would these folks be excluded from ICER modelling with only those with positive preference scores are allowed? Is this a two stage exclusion process: first, eliminate those with EQ-5D-5L health states worse than death and, second, eliminate those on the results of the QALY thresholds and budget based access limitations?

CONCLUSION

All ICER claims for pricing and access, even though nonsensical, are merely placeholders, subject at any time for assumption driven revisions. Given the number of assumptions, any can be challenged by real world data driving a new assumption claim; although still not a claim on the future. These real world data need not meet the standards for fundamental measurement; they can be 'new' ordinal preferences or new patient reported outcomes (PTROs) which also fail the standards of fundamental measurement.

For those who with ICER are committed to this analytical dead end, the continued mining of real world data to support an ongoing process of assumption modification across multiple disease areas, must be something of a flux to look forward to in eager anticipation. More appropriately, the question is: why waste time constructing these assumption driven simulations in the first place? They are manifestly pseudoscience, adding nothing to establishing credible value claims, the discovery of new yet provisional facts, that can be empirically evaluated and replicated. If claims are only an invented placeholder yet subject to a possibly endless process of assumption modification and claims adjustment then they have no place in decision making for the allocation of health resources; it seems best to ignore ICER as a fantasy exercise. For those seeking to challenge rather than ignore ICER the answer must be to hold your breath and wait for the next installment of real world evidence based assumption modification. This may even result in ICER recommending price increases!

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