THE TRUTH IS OUT THERE: ICER'S COMMITMENT TO IMAGINARY APPROXIMATE INFORMATION

One of the most intriguing aspects of the commitment by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and its acolyte the Institute for Clinical and Economic Review (ICER) is the creation of approximate information. Rather than emulating the physical sciences and other social sciences, health technology assessment has turned its back on hypothesis testing in a commitment for the discovery of new, yet provisional and unevaluable, facts. For the followers of ISPOR and ICER, evidence to support formulary decisions is created through imaginary simulation modeling, not through the standards of normal science. This is not a sound basis for formulary decisions. We need to reconsider our priorities and commit to programs of evidence assessment in rare and chronic diseases.

The Pseudoscience Position

Over the past several years, ICERWatch has worked to hold the Institute for Clinical and Economic Review (ICER) accountable and demonstrate that the construction of cost-per-QALY reference case imaginary worlds is not only a futile endeavor but an unwanted and unnecessary distraction for formulary decisions. This point has also been made in commentaries that have appeared over the last few years in the University of Minnesota journal *Innovations in Pharmacy*.

Attempts to take this message to a wider audience comes up against an entrenched belief in the role of imaginary or approximate evidence as the driver for formulary decisions. This position, which is endorsed by groups in the US such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) together with agencies like the National Institute for Health and Care Excellence (NICE) in the United Kingdom and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, has dominated the health technology assessment value frameworks for decades. This belief is widely shared by academic groups and the leading academic journals in the field to the extent of effectively excluding any criticisms of the dominant meme to appear in print. The Boston-based ICER is merely an expression of this commitment to approximate information created by the construction of imaginary worlds.

Defending the Indefensible

The dominant meme in health technology assessment, as evidenced by the ICER reference case, is easily demolished. It clearly fails the standards of normal science. The focus on creating 'evidence' excludes the commitment that characterizes normal science: confronting theory with evidence. Rather, the ICER

commitment is to a succession of imaginary worlds with one set of non-evaluable claims replacing another. For ISPOR and ICER imaginary evidence trumps real world evidence. We believe in our mythical constructs. Even when there is a belated acceptance that other factors – possibly "patient centric" – might be considered in formulary decisions and value assessments, the imaginary cost-per-QALY modeled claims still take center stage.[1]

The indefensible ICER model is challenged and defeated on two grounds: first, from the standards of normal science the lifetime model fails to meet standards for credibility, evaluation and replication and, second, the QALY construct is a mathematical impossibility. The ICER approach therefore founders at two levels of ignorance: the standards of normal science and ignorance of the role of fundamental measurement in the testing of hypotheses where generic utilities, manifest scores, are applied to time spent in a disease stage to create a QALY. This denies the axioms of fundamental measurement as the EQ-5D-3L, for example, creates utilities that are on an ordinal scale; to multiply you need a ratio scale.[2] We have known this formally from the seminal work of Stevens 75 years ago.[3] Repeated efforts to get this message across in health technology assessment have fallen, so far, on deaf ears.[4] [5] Interestingly, although ISPR has devoted considerable time and effort to discussing alternative value frameworks, there has been no mention of Rasch Measurement Theory (RMT)[6] and its ongoing contribution to developing needs-based quality of life instruments; despite papers in leading journals (even *Value in Health* in 2004)[7] on the fundamental measurement problems of generic utilities and proposals for evidence based claims in therapy response.

Approximate Information

A recent ISPOR task force report on value assessment makes quite clear that: *Leaders in the field of economic evaluation in health care have long recommended that analysts seeking to inform resource allocation decisions approximate the value of interventions in terms of incremental cost per QALY gained* [emphasis added].[8] While this may sound laudable, deconstructing it points to some issues the task force did not address. First, it is not clear what "inform" means. Does it mean just presenting a cost-per-QALY claim or, in the case of ICER, making recommendations for pricing and access? Second, the term "approximate the value" is not defined; approximate in relation to what value? Third, the ubiquitous QALY; the task force does not appear to recognize, or perhaps it's a reluctance to admit that the QALY is an impossible construct. It rests on the disallowed application of utilities to create the QALY construct as the utilities are only raw scores.

Understandably, ISPOR would be reluctant to admit that the QALY lacks any credibility as a construct, let alone as the basis for constructing value claims. As they point out: Thousands of cost-per-QALY analyses have been carried out and catalogued; the latter in what has been described as the Tufts utility emporium – a database that allows you to choose a utility by disease and subject characteristics. Thousands of ordinal manifest scores to be interpreted as measures that have ratio properties.

It is not clear how formulary committees, who are well versed in the evaluation of Phase 2 and Phase 3 pivotal trial data, would respond to a joint announcement by ISPOR and ICER that what they are providing, in modeled cost-per-QALY claims, is a modeled mirage. A value assessment framework that fails the standards of normal science and, to cite Piglucci's felicitous phrase, is pure bunk.[9] While ICER may respond that the model is "realistic" in its choice of assumptions and is swaddled in scenarios and sensitivity analyses to address issues of uncertainty, the unfortunate fact is that the model is an illusion; merely one of any of a potential multiverse of other worlds, none of which would have any claim to be more

"realistic" than another and none of which would meet the standards of normal science. There could be any number of competing ICERs, funded by opposing groups, with each claiming the high ground in approximate information with a cost-per-QALY value framework in common.

All Swans are [Not] White

To claim that the assumptions that typically underpin the ICER modeled imaginary world are "realistic" is clearly ridiculous. It has been made clear, from the seminal contribution of the philosopher David Hume (1714-1776), that we cannot assume that because on observation has held in the past it necessarily holds in the future. Past observations cannot support future claims. Yet this is what ICER asks us to believe. This overlooks Hume's problem of induction: all swans are while, until your vacation in Western Australia with your second trophy husband, a builder of ICER imaginary worlds, that swans can also be black. Empirical generalizations, while not verifiable, **are** falsifiable. Knowledge doesn't grow from generalizations. As put so succinctly by Magee: We cannot secure an assumption from prior observation, nor can we observe future events. We cannot secure it by logic since from the fact that all past futures have resembled past pasts it does not follow that all future futures will resemble future pasts.[10] In short, the ICER modeled by assumption claims are unacceptable.

The Truth is Out There

If we are claiming that the reference case cost-per-QALY models generate critical approximate information, then it's reasonable to ask: approximate to what? Is there, in some paranormal *X Files* sense, a "model" or "accurate replication of the future"? Or even some Platonic abstract of the ideal, that capturing the known and unknown evidence to support its true "assumptions" is capable of generating "true" lifetime incremental cost-per-QALY claims? If so, then this paranormal construct can presumably override the axioms of fundamental measurement with the creation of "pure" QALYs.

Clearly, this is nonsense but it raises a basic philosophical question: if there is no reference point for "true" information regarding cost-per-QALY reference case claims, then how can we claim that our various models "approximate" that information? Perhaps ICER is so far out in an imaginary playing field that whatever it claims should be treated as improbable nonsense. It has not only dropped the ball, but has yet to recover it. The concern, from an evidence-based medicine perspective, is that formulary decisions will be based on imaginary value claims; how do we distinguish "approximate information" from "approximate disinformation'"?

The only escape is to argue that the information is approximate because the assumptions driving the modeled claims are "approximately" realistic. Yet, we have the role of imaginary world cost-per-QALY academic assessment groups that have emerged – University of Sheffield in the UK, and the University of Adelaide in Australia. These groups are tasked with challenging manufacturer's imaginary models on their structure and choice of assumptions. Where necessary, they create an alternative and "improved" imaginary world. Presumably, this produces more approximate "approximate information." While this may seem a pointless exercise, organizations such as NICE in the UK and the PBAC take these imaginary academic exercises seriously.

If the ISPOR-embraced role of approximate information collapses, we are left with competing interests bickering over competing imaginary constructs.

Those Who Believe

Convincing those in health technology assessment that the cost-per-incremental QALY value assessment framework is a mathematical impossibility and one that fails the standards of

normal science is difficult. A belief that has been held for over 30 years will not surrender its role in formulary evaluations lightly. In the US there are many healthcare systems that have endorsed the ICER value assessment framework. Many of these also support ICER directly. These include Harvard Pilgrim Health Care, AETNA, Anthem, Blue Shield of California, Express Scripts, Kaiser Permanente, and United Healthcare.

Next Steps

Perhaps there is only one step: abandon the constriction of imaginary worlds. Abandon fabricated imaginary information for a program of real-world evidence in therapy and disease areas. But this would mean abandoning ICER – welcome and productive outcome, given its commitment to reference case imaginary claims.

Even if it was pointed out – and repeated on numerous occasions – that from the perspective of normal science, the ICER reference case is a faerie nonsense, ICER would persevere. It has no option if it is to convince its financial backers. Its business model depends on creating approximate information and convincing formulary committees that this is unequivocally "the state of the art" in health technology imaginary, evidence-free evaluations.

Once formulary committees and other health care decision makers recognize this charade, the better. Ending this charade gives hope that we can move formulary decisions from "imaginary world evidence" to "real world evidence."

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