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THE INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW'S (ICER's) DENIAL OF ADUCANUMAB IN ALZHEIMER'S DISEASE

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Abstract

The release of the ICER evidence report on Aduhelm (aducanumab) in Alzheimer's disease today (August 5 2021) gives ample confirmation that ICER is committed to creating evidence to support recommendations for pricing and access [1]. ICER's recommendations for pricing and access to Aduhelm should be rejected out of hand; they are a based on a discredited analytical framework that denies the standards of normal science and endorses a QALY which is a mathematical impossibility[2] [3]. ICER is well aware of these criticisms, but chooses to ignore then as the QALY is critical to their business case. The Alzheimer's report continues the long-standing belief by ICER in pseudoscience; the construction of assumption driven modelled simulation of cost-per-QALY claims to support denial of access to care. Evidence is invented to support claims for social pricing with the effect of denying access to care and potentially discouraging investments in clinically effective Alzheimer's therapies.

INTRODUCTION

The Institute for Clinical and Economic Review (ICER) is well aware of the many criticisms of its commitment to inventing evidence through simulation modelling; yet holds to this belief in imaginary claims that share the stage with intelligent design. Yet ICER perseveres for one simple reason: it is their business model. If ICER acknowledged these criticisms, which they have rejected out of hand, then all evidence reports would have to be withdrawn, including the latest report on Alzheimer's disease. Instead, ICER argues that are only doing what is the standard (or meme) in health technology assessment, even though it fails the standards of normal science. ICER endorses the role of imaginary models; unfortunately, Imaginary models lead to imaginary claims.

DENIAL OF NORMAL SCIENCE

ICER's denial of the standards of normal science, including the established standards for measurement, is all too obvious in their defense of their Aduhelm modelling. Certainly there is a clinical debate over the merits and place of this biologic in the treatment of Alzheimer's disease; a debate however which is not improved by ICER inventing evidence to support imaginary recommendations for Aduhelm pricing and place in therapy. This is a major disservice to providers, patients and caregivers in this debilitating disease. Even so, many who are totally ignorant of the limitations of the ICER analytical framework, would latch on to these imaginary claims to support pricing and access negotiations. Whether ICER is right or wrong is beside the point; it is a useful pitch in a negotiation by insurers and others. This is why it is imperative to maintain the pressure on ICER through informing prospective audiences who might be

tempted to believe in imaginary constructs, subject to the ministrations of insurers and health system decision makers. To apply a well-worn cliché: if ignorance is bliss, 'tis folly to be wise. After all, belief in imaginary simulations and ICER is the soft option.

The ICER approach to pricing and access for pharmaceutical products, its perceived place as the self-appointed national arbiter for health technology assessment in the US, is a sham [4]. Rather than providing a coherent evaluation that meets the standards of normal science, ICER descends into pseudoscience. The claims made are no better that those for intelligent design. If you want to make credible claims then they have to be built on a framework where those claims can be empirically evaluated. This is the essence of drug discovery. Unless the QALY and cost claims by ICER for Aduhelm's place in therapy are credible and empirically evaluable, then they should be ignored. In its rush to be first cab off the rank to review and assess cost-effectiveness for newly FDA authorized pharmaceuticals, ICER relies on the soft option of inventing evidence; rather than the harder task of proposing a detailed research program to meet evidence gaps before jumping to conclusions; thus effectively slamming the door on future evaluations.

But the rot goes even deeper; none of the claims made by ICER for Aduhelm can be accepted because they are created by an assumption driven simulation model that is designed to produce non-evaluable claims; assumptions from the past that, illogically, are seen as claims to hold in the future. This is the ICER safe harbor; no ICER claim or recommendation can be challenged empirically for Aduhelm. This puts companies in an unenviable position in making a case for the place of their product in therapy at a price commensurate with ongoing investment. Unfortunately, any number of competing simulations can be created by varying assumptions. A cynic could reverse engineer the ICER model to come to opposite claims for Aduhelm, but ones equally impossible to empirically assess. ICER has no incentive with the risk of ridicule to overturn the results of its modelling to revisit the imaginary claims for Aduhelm. As this would involve, presumably, revised assumptions to populate yet another imaginary simulation the effort would be a waste of time.

DENIAL OF MEASUREMENT STANDARDS

Apart from denying the application of the standards of normal science, ICER continues to believe in standards of measurement which were discredited over a century ago; indeed were rejected as far back as the scientific revolution of the 17th century (for which ICER had not, apparently, received the memo)[5]. Taking our cue from the physical sciences, measurement of attributes such as quality of life (or temperature, weight) must be designed to have these properties. That is, they must be measures that have ratio or interval properties, as well as the property of unidimensionality. What this means is that measures must not be capable of creating negative scores or values; it must have a 'true zero'. The ICER model collapses because the preference scores, from instruments such as the EQ-5D-3L or EQ-5D-5L that are central to the construction of QALYs, all produce negative 'worse than death' health states. The latest attempt to value health states defined by the symptom and response levels pf the EQ-5D-5L concluded (for the US) that 20% of health states defined by the instrument are 'states worse than death' with scores in the range -0.573 to 1.0 (where death = 0 and 1 = perfect health) [6]. Should health care be denied to patients who have negative scores for their reported health state? Would ICER argue for

denial of care in these patients? Undoubtedly yes; otherwise why invent contrary evidence for pricing and access. In practical terms, ICER will be unlikely to agree to any disease specific evaluation program in Alzheimer's disease for the simple reason that it would provide a counterfactual critique of the ICER generic, one size fits all, preference driven assumption simulated cost-per-QALY models. The two approaches are incompatible; ICER has too much to lose. The ICER imaginary simulation business model trumps any commitment to the standards of normal science. We cannot expect ICER to engage in developing a research program to support the introduction of therapies to address therapy response in Alzheimer's disease.

It should be remembered that, in the physical sciences, measurement always refers to single attributes with ratio properties. This is why multiattribute instruments such as the EQ-5D-3L/5L are impossible measures, yielding only ordinal scores. They are constructed from single attributes (pain, anxiety/depression) which are ranked ordinally and lack unidimensionality. The aggregate score therefore lacks dimensional homogeneity and construct validity. It is a dog's breakfast.

The presence of negative scores also means that the preference score is ordinal (not ratio) and that the QALY, as it involves multiplying time by this ordinal score, is a mathematically impossible construct (the QALY would have a negative value). ICER is aware of this but insists, by some mystical alchemy, that even with negative scores it is a ratio scale, in an apparently effective disguise, to justify creating QALYs [7]. ICER must, however incoherently, cling to this strange belief which involves assuming that lifetime imaginary QALYs and cost-per-QALY thresholds have meaning in health decision making and are 'true measures' for patients and caregivers in Alzheimer's disease. They are not. In consequence this has potentially adverse implications not only for patients in Alzheimer's disease (and their caregivers) but all the other drugs in disease states that ICER has reported on over the years.

Fortunately, we have an option that can be easily applied to one of the often ignored aspects of Alzheimer's disease (and ignored by ICER) the quality of life of caregivers, both spousal and non-spousal. If new therapies are introduced, a critical question is whether or not the quality of life of caregivers is improved for the various stages of Alzheimer's disease. This has been addressed in the development of the APPLIQuE measure [8]. This is an instrument that meets the required measurement standards and creates an interval score to assess response to therapy. More recently, an algorithm has been developed to translate these scores to a bounded ratio scale of need fulfillment: the need or N-QOL scale [9]. This allows a quantitative assessment of the extent to which the need of spousal caregivers are impacted by the introduction of new therapies; a value claim which provides a robust assessment of response to therapy. The transformation algorithm can be applied to over 30 disease states with already developed instruments to assess response to therapy.

DENIAL OF HEALTH CARE

But there is a darker side to the ICER application of societal preferences to the allocation of healthcare resources: the role of cost-per-QALY thresholds to deny access to care [10]. Denial of care through societal preferences has a long and disturbing history in eugenics; the exclusion of people who are not, by societal preference or political decisions, deemed 'worthy'; they are experiencing 'inferior' health states.

We thought we had discredited eugenics: the exclusion of people or groups judged to be inferior, but ICER brings it back through the back door with societal preferences for 'worthy' and 'less worthy' health states. This is seen in ICER's embrace of societal preferences for health states, with instruments such as the EQ-5D-3L/5L to construct QALYs. ICER does not report how many patients and caregivers experience negative scores in Alzheimer's disease, these are hidden in the application of average preferences (where averages of ordinal rankings are mathematically impossible). These preferences enter the ICER imaginary calculus for QALY thresholds where an adverse imaginary cost-per-QALY threshold can justify ICER recommendations for denial of care and absurd recommendations for pricing reductions (the strange notion of a societal Benefit Price Benchmark which defies the standards of normal science and measurement theory). Imaginary benchmarks are of particular concern in rare diseases where ICER thresholds and claims for an imaginary social price may discourage investment and access to care. Of course, the ICER preference modeling is pseudoscience; but so is eugenics. Yet both can have substantial adverse consequences.

CONCLUSIONS

ICER is well aware of these criticisms but continues to see itself as the arbiter of care access, just as policy makers embraced the pseudoscience of eugenics in healthcare resource allocation, ICER tries to convince policymakers to embrace the pseudoscience of imaginary QALY thresholds. To be honest, Biogen and other manufacturers in Alzheimer's and other therapies should not demean themselves by even engaging with ICER. At best, manufacturers might perhaps offer the services of a shredder. But ICER will not change. If you are facing an analytical dead end, there is nowhere to go but to continue the assumption driven imaginary evidence mantra that we are only doing what others have done. Perhaps ICER might think outside of the box and offer constructive advice on how evidence gaps to make believable quality of life claims might be filled rather than inventing evidence; but this would be to admit defeat. As it stands the model claims are non-evaluable; we don't know whether they are right or even wrong, we will never know and were never intended to know. Welcome to the magical ICER world of formulary decisions in the 21st century; decisions driven in large part by a failure to recognize by all too many health care decision makers the absurdity of the ICER paradigm for inventing superficially plausible yet imaginary claims.

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