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More Unnecessary Imaginary Worlds: The Institute for Clinical and Economic Review's Final Evidence Report and Recommendations for Acute Migraine Therapies

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Abstract
On 25 February 2020, the Institute for Clinical and Economic Review (ICER) released its final evidence report for acute migraine therapies. The report found that on the clinical evidence that these therapies improved function compared to placebo with a moderate certainty of a small or substantial health benefit. Even so, on the basis of a cost-effectiveness modeling, a two year modified Markov model, ICER concluded that the benefits offered over existing therapies were minor. The result was a series of recommendations for WAC price discounting, with the major impact on the Lilly therapy lasmiditan (Reyvow). ICER recommended prior authorization for all three therapies (lasmiditan, rimegepant and ubrogepant. The purpose of this commentary is not to consider the comparative clinical basis for competing efficacy claims (for which the evidence is limited) but to consider incremental cost-per-QALY modeled claims. These, as has been the case of previous ICER evidence reports, fail to meet the standards of normal science. Constructing an imaginary world with QALYs that fail to meet the standards of fundamental measurement does not advance our discovery of new facts; it recycles old assumptions. The pricing and prior authorization recommendations of the evidence report must be rejected. Given the two year time frame for the model, ICER would have been better employed to press for a research program to assess the relative benefits of these competing therapies. This program could have been implemented and reported within a two-year time frame. As well, ICER could have considered developing one of more needs-based migraine instruments that met Rasch measurement theory standards. This will not happen. Rather we see ICER as continuing to support imaginary cost-per-QALY worlds and then bringing in possible research proposals. A progression, if you like, from imaginary world evidence to real world evidence, where the former always takes precedence. After all, it is the ICER business model.

Keywords: imaginary worlds, migraine, ICER, pseudoscience, nonsense claims, nonsense recommendations

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Introduction

The construction of assumption driven imaginary worlds to support incremental cost-per-QALY claims for pricing and access recommendations is the hallmark of the Institute for Clinical and Economic Review's (ICER) business model. On 25 February 2020 ICER released its final evidence report for three acute migraine therapies. These comprised two calcitonin gene-related peptide (CGRP) antagonists ubrogepant (Ubrelvy; Allergan) and rimegepant (under FDA review; Biohaven Pharmaceuticals), and a selective 5-HT 1f agonist lasmiditan (Reyvow; Lilly).

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The purpose of this commentary, as part of a series of critical assessments of the ICER value assessment and reference case methodology, is to make clear that the recommendations for pricing and access should not be taken seriously. It is not the purpose to review the clinical case presented by ICER, but to alert decision makers that the value assessment framework, the reference case model fails the standards of normal science.

The ICER Simulated Claims

ICER's modeled cost-effectiveness is based on a semi-Markov model with time varying proportions of patients with response to therapy. The model cycle was 48 hours based on typical duration of trials evaluating migraine treatments. Two hypothetical cohorts of patients were simulated: (i) all treated with lasmiditan, rimegepant, ubrogepant or usual care and (ii) all treated with lasmiditan, rimegepant, ubrogepant, sumatriptan or eletriptan. Under (i) each therapy was compared to each other with no migraine additional migraine specific acute treatment. Under (ii) the first three therapies were compared to each other and to the two triptans. Patients entered the model either as 'on treatment, no migraine' or 'on treatment with migraine'. Treatment outcomes were evaluated at four time points: 2, 8, 24 and 48

hours. Discontinuation was allowed. Outcomes from the simulated model were: cost per quality adjusted life year (QALYs) gained, life years gained, equal value of life years gained and cost per hour of migraine pain avoided. Within each cycle the proportions of patients with severe, moderate, mild or no pain was evaluated at baseline and at each of the following four time points. A two-year time horizon was assumed to be sufficient for simulating cost-effectiveness of acute treatments. Discounting was at 3%.

Given the time-horizon for the model simulation, differences over usual care for QALYs (identical to equal value of life years gained) were minimal. In the case of QALYs the two CGRP antagonists yielded, as would be expected, the same incremental QALYs, over usual care of 0.015 with 0.011 for lasmiditan. Life years were, not surprisingly, identical for all populations. Hours of pain were 2,100 for usual care, 1,740 for lasmiditan, 1,580 for ubrogepant and 1,570 for rimegepant. In the model with sumatriptan and eletriptan, the two triptans dominated the other therapies with simulated higher QALYs at a lower cost.

Cost per QALY gained, only reported for the first population (as the triptans dominated the second) against usual care were: (i) lasmiditan $177,500; (ii) rimegepant $39,800; and (iii) ubrogepant $40,000. Cost per hour of pain avoided were, respectively, $5.47 and $1.15 for the CRGP antagonists. In consequence, price discounts from WAC to achieve threshold prices were in the range: lasmiditan 32% to 40%, and for the two CRGP antagononists 5% - 15% (rimegepant assumed to have same price as ubrogepant)

As detailed in this commentary, these simulated results should not be taken seriously. More to the point it seems strange that ICER would go to the trouble of developing 2-year simulated claims rather than putting imaginary constructs to one side and establishing protocols and hypotheses for comparative product performance. The exception here would be QALYs. Claims for cost per QALY would not be made because the EQ-5D fails to meet the axioms of fundamental measurement; it is an ordinal manifest score.

Nonsense on Stilts

A recent commentary in INNOVATIONS in PHARMACY reviewed the latest ICER VAF to be applied over the period 2020 to 2023 [1]. The commentary concluded that the VAF failed to meet the standards of normal science; it was considered pseudoscience. The principal reason for the ICER VAF failing the demarcation criteria between science and pseudoscience (or pure bunk) was its rejection of modeled claims that allow empirical evaluation. At the same time, the ICER VAF fails the standards for fundamental measurement [2]. It applies utilities which are manifest scores, they have ordinal rather than interval scale properties. This means that the consequent QALY and cost-per QALY estimates are meaningless. The consequences are, for products in migraine, that conclusions regarding estimated value and proposals for lifetime cost-per-QALY, with consequent recommendations for price discounting are just snake oil. They are an unnecessary illusory distraction, irrespective of the degree of precision presented.

The purpose of this commentary is to build on the analyses and arguments presented in previous commentaries, notably the review of the ICER 2020-2023 VAF, to make the case for rejecting the draft evidence report on migraine. The commentary starts with a brief restatement of the role of normal science as a process of discovering new facts; not recycling old assumptions. This is followed by a rejection of ICER's fabrication of an imaginary future sickle cell treating environment as simply one of any number that could be created with varying assumptions. After all, the accepted framework in health technology assessment which ICER accepts is to reject hypothesis testing in favor of 'approximate information' (whatever that means for an unknown future) [3].

Given ICER's emphasis on QALYs and the fabrication of incremental cost-per-QALY claims, the next step is to point out the failure of ICER to grasp that if utility scores are to be applied to estimate time in disease states, then they have to meet the fundamental axioms of measurement theory: invariance of comparisons and sufficiency. They have to reflect an underlying construct of relevance to the target patient population with unidimensional and interval scoring properties. The EQ-5D utilities that ICER relies upon in fabricating claims in migraine do not meet these standards. The QALYs are nonsense.

Finally, we point to the importance of constructing claims for treatment response within disease areas; not utilizing a generic health related quality of life construct (the EQ-5D) that captures a limited number of symptoms and ordinal responses. The case made here is for a latent needs-based construct, where the instrument reflects the needs of patients in migraine, and if required a separate instrument for the needs of caregivers. These should meet Rasch measurement theory standards. This is an unexceptional requirement that has been in place for 60 years in the application of Rasch Measurement Theory (RMT) to instrument development[4]. Unfortunately, those developing the EQ-5D utility system failed to receive the memo. ICER appears to be in the same boat.

In achieving these objectives, it should be emphasized that deconstructing an ICER incremental cost-per-QALY model does not imply support for the imaginary world meme. While the construction of imaginary worlds has been the mainstay of health technology assessment claims over the past 30 or more years, ICER's plea that it is applying 'state of the art; techniques' is both misleading and irrelevant.

Constructing imaginary evidence, as considered in more detail below, is not how science advances, particularly when the claims for QALYs are nonsensical. They fail the axioms of fundamental measurement. They should be abandoned. Rather, as in drug development, technology assessment should be a process of discovery, not a process of fabricating one imaginary construct after another with various non-evaluable claims and value judgments. ICER, as noted in previous commentaries is an irrelevant and unnecessary distraction; unfortunately, against all common sense, ICER will be determined to persevere in the marketing of imaginary models and recommendations.

The Standards of Normal Science

The requirement for testable hypotheses in the evaluation and provisional acceptance of claims made for pharmaceutical products and devices is unexceptional. Since the 17th century, it has been accepted that if a research agenda is to advance, if there is to be an accretion of knowledge, there has to be a process of discovering new facts. By the 1660s, the scientific method, following the seminal contributions of Bacon, Galileo, Huygens and Boyle, had been clearly articulated by associations such as the Academia del Cimento in Florence (1657) and the Royal Society in England (founded 1660; Royal Charter 1662) with their respective mottos *Provando e Riprovando* (prove and again prove) and *nullius in verba* (take no man's word for it) [5].

By the early 20th century, standards for empirical assessment were put on a sound methodological basis by Popper (Sir Karl Popper 1902-1994) in his advocacy of a process of 'conjecture and refutation [6] [7] . Hypotheses or claims must be capable of falsification; indeed, they should be framed in such a way that makes falsification likely. Life becomes more interesting if claims are falsified because this forces us to reconsider our models and the assumptions built into those models.

Although Popper's view on what demarcates science (e.g., natural selection) from pseudoscience (e.g., intelligent design) is now seen as an oversimplification involving more than just the criteria of falsification, the demarcation problem remains [8]. Certainly, there are different ways of doing science but what all scientific inquiry has in common is the 'construction of empirically verifiable theories and hypotheses'. Empirical testability is the 'one major characteristic distinguishing science from pseudoscience'; theories must be tested against data. We can only justify our preference for a theory by continued evaluation and replication of claims. Constructing imaginary worlds, even if the justification is that they are 'for information' is, to use Bentham's (Jeremy Bentham 1748-1832) memorable phrase 'nonsense on stilts'. If there is a belief, as subscribed to by ICER, in the sure and certain hope of constructing imaginary worlds, to drive formulary and pricing decisions, then it needs to be made clear that this is a belief that lacks scientific merit.

Assumptions

The ICER claim to fame is the ability to construct or fabricate an imaginary world that sets the stage for value impact over 10, 20 or 30 years in the future. In the ICER migraine model, the number of assumptions made to support the microsimulations across the four patients groups is truly awesome; some come from the literature, others are pure guesswork. This is acknowledged by the modelers where they make quite clear that there are 'gaps' in data on which to create assumptions (e.g., *Since the absolute effectiveness gains of patients remaining 'on treatment, with migraine' Markov state is not known, this estimate was subject to a modifier that was set at 56% of full benefit for the base case.* [pg. 56})

Unfortunately, even if an assumption driving the imaginary value assessment framework is defended by appealing to the literature (including pivotal clinical trials) the effort is wasted. The point, and this goes back to Hume's (David Hume 1711 – 1776) induction problem, is that we cannot ask clients in health care to believe in models constructed on the belief that prior assumptions will hold into the future. It is logically indefensible: 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*' [9]. Claims, for the relevance of a constructed imaginary world built on the assumption that the model elements have been validated by observation is simply nonsensical.

Certainly, models can involve assumptions but the difference is that the worth of the assumptions can be assessed if the model is designed to generate evaluable, credible and replicable claims. Clearly, the ICER VAF model is designed to accomplish precisely the opposite. Formulary decisions should not be based on a mélange of assumptions.

Utilities and QALYs

Quality adjusted life years (QALYs) can only survive if the measure is credible, evaluable and replicable. The QALY constructed by ICER meets none of these criteria. The concept of a QALY is not new; it goes back some 40 plus years with the notion of combining time spent in a disease state with some multiplicative 'score' on a required interval scale of 0 to 1 (death to perfect health), Combining the two, multiplying time by utility is assumed to produce a QALY. In the ICER imaginary migraine world these are combined to produce QALYs for the modeled life span.

Unfortunately, a point that neither ICER nor the contracted model builders have recognized, is that the utility system used, the EQ-5D, has only ordinal properties. The utility scores are simply manifest scores. They are ordinal because we cannot say what the quantitative difference is between the scores. A utility of 0.5 versus a utility of 0.6 may appear to have interval properties, but we cannot add or subtract these

values, let alone multiply with them. All we can create are medians and modes. Mean estimates are ruled out. The reason is clear: the EQ-5D system was not designed to have interval properties; by default it is an ordinal scale.

Certainly, it is possible to see if, by happenstance, the EQ-5D scores for a target patient group have interval, unidimensional properties. The evidence, for the few times this has been attempted, is not convincing. Unless ICER, each time it utilizes the EQ-5D system, or other utility system in a model, is able to demonstrate unidimensional properties (Rasch standards), then it must be rejected. In the case of migraine, ICER and its contracted model group must be able to demonstrate Rasch measurement properties for each hypothetical patient group modeled with EQ-5D scores. Absent such an assessment for unidimensionality and interval properties, the model for each migraine group collapses. QALYs and consequent incremental cost-per-QALY claims have no meaning. The application of threshold values and recommendations for WAC price discounts are meaningless.

HRQoL versus QoL

ICER takes a social or population perspective in its modeling. To do this it has to rely on ordinal generic systems such as the EQ-5D. It can't fall back on a disease specific model for a target population as this would undercut the cost-per-QALY threshold applications. Comparisons between disease states require generic utilities. As these are manifest scores, this is an impossible undertaking. Adopting a QoL instrument with interval scoring properties would negate this business model. Indeed with a disease specific QoL index, QALYs would have to be abandoned.

It should be remembered that the EQ-5D is a health related quality of life (HRQoL) measures. It comprises 5 symptoms (select by an expert panel) and 3 response levels for each symptom (the EQ-5D-3L) or five response levels (the EQ-5D-5L). The latter is considered more responsive, but is for all intents and purposes a different system as it yields quite different 'utility' or manifest score profiles. In the case of both EQ-5D instruments, the 'ordinal scores' (the 'values') are generated by an algorithm where the preferences or weights for each response are determined by a population sample; not patients in a specific disease state. Responses by patients are weighted to give a manifest raw score that reflects the preferences of the US population for the symptoms and response levels reported by patients in a disease state. The problem, of course, is that a change in response 'level' from one manifest score to another (distance unknown) may reflect what clinicians see as a therapeutic benefit, but fail to meet the required standards of instrument calibration.

The fundamental weakness is that HRQoL symptom/response instruments have only a tenuous, if any, link to a latent construct. They, in fact, represent a mishmash of possible health constructs, where each symptom category might represent a latent construct. It is an operational measure, not one that bears even a limited relationship to a patient-centric measure of QoL.

Since the early 1990s, increasing attention has been given to QoL versus symptom and response characterizations of HRQoL in evaluating the benefit to patients of innovative therapies [10]. Rather than imposing a series of potential symptoms and responses, the needs approach starts from a simple premise: the focus should be on QoL as a single latent construct; one which is disease specific (and specific to patients and caregivers) which is defined in terms of the needs of target groups. If health and disease status are the principal driver of 'good health' in QoL, then we have to identify those needs and devise an instrument that captures those needs in a single index with interval properties for target patient and caregiver groups.

Surprisingly, perhaps to ICER, the tools to achieve instruments with these properties, conforming to the axioms of fundamental measurement, have been available, and widely applied in the past 60 years through RMT [11]. We have an armory of these instruments specific to disease states suitable for assessing therapy response. Imaginary QALYs are an analytical dead end.

QoL in Migraine

Paying attention to ICER imaginary modeled claims for pronouncements on pricing and access in acute migraine therapies is clearly nonsense. It is not just a question of the ICER model being only one of many alternative models to construct imaginary claims in migraine therapy but its denial of the patient voice. We should put HRQoL measures to one side in favor of migraine specific QoL measures; one's that meet RMT standards.

Unfortunately, while there are a number of migraine specific HRQoL and QoL instruments available, none meet the required RMT standards. They may meet the standards for classical test theory, but fail to go that extra step to meet the requirements of the Rasch model. The more widely used models are the Migraine Specific Quality-of-Life Questionnaire (MSG Version 2.1) with its three-factor latent structure which, while providing manifest scores to give a broad picture of change from baseline (proportions in ordinal response categories) still fails to meet Rasch standards for unidimensionality and interval scoring on a single index [12] [13]. The same objections would apply to the Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) and to the more widely used Migraine Disability Assessment (MIDAS) instrument, which is best characterized as HRQoL rather than QoL [14] [15] [16].

Perhaps the one instrument, which was not developed to meet Rasch standards, that comes closest to a needs-based construct is the Migraine Specific Quality of Life

Questionnaire (MSQoL) [17]. Developed by McKenna et al of Galen Research, who have since developed, RMT standard instruments in a variety of disease states, this instrument takes a need-fulfillment perspective; explicitly rejecting functionality and instruments developed by physicians, the items were developed from qualitative patient interviews, with the emphasis on providing an index. A particular focus of the instrument was for assessing the effects of migraine on the patient between attacks.

Of course, ICER is caught between the proverbial rock and a hard place. This is why it rejects patient-centric measures in cost-effectiveness evaluations. It has to use a generic utility measure (flawed as it is) to support the fabrication of imaginary QALYs; absent a generic utility measures (or at least a manifest score on a 0 – 1 metric), QALYs cannot be modeled and the exercise collapses. ICER has no option; it has to use the EQ-5D HRQoL instrument even though it may have no relation to the concerns of patients apart from failing the axioms of fundamental measuremet. ICER is then open to continuing criticism that its models for value assessment are just 'nonsense on stilts'. This applies to the migraine reports as well as to its other evidence reports. One possible escape for ICER is to propose, after the imaginary migraine evidence model has been constructed and pricing and access recommendations presented, to suggest a move to *real* world evidence (from *imaginary* world evidence) and a possible disease specific research program (see below). The first step seems redundant; but it is the ICER business model.

Approximate Information (or disinformation)

Apparently, according to ISPOR, the leaders in health technology assessment have laid down, asserted a dogma, that modeled incremental cost-per-QALY claims are the gold standard, not for testing hypotheses which are impossible for claims 30 years into the future, but to fabricate 'approximate information'. Apart from the obvious point that, if a formulary committee is faced with competing 'for information' claims in migraine it will have concerns over choosing one set of claims over another, the phrase 'approximate information' defies common sense. Certainly we can talk of approximating a measure. After all, the key to scientific progress is having accurate measurement. Without accurate, standardized and agreed instrumentation we would be back in the 17th century; the same holds for the social sciences where for non-physical constructs such as needs based QoL we need to build instruments with agreed measurement properties.

For ISPOR and ICER instrumentation is put to one side (along with hypothesis testing). Rather we are satisfied with 'approximate information'. Unfortunately, looking ahead 30 years in the sure and certain hope of our imaginary constructs creating approximate information we have no idea what 'approximate' means.

The migraine cost per QALY presentation points to the 'flexible' nature of ICER cost-per-QALY calculations. The greater the difference in the number of incremental lifetime imaginary ordinal OALYs, the greater the price that can be justified. Conversely, the lesser the difference, if this can be 'fabricated', the greater the recommended discount. This is exemplified in the ICER migraine model. Putting to one side the amazing number of literature referenced and 'by guesswork' assumptions needed to create the microsimulation imaginary model, the end result is an "ICER certified" approximate information (or disinformation) model to support pricing and access decisions in migraine.

As this review of the source of EQ-5D utilities has shown, it is always important to 'deconstruct' an ICER modeled imaginary world. Assumptions are important as they are the basis for the VAF. Utilities are a key assumption and the often convoluted steps taken to construct them, defying any standards of fundamental measurement, are typically a little odd. Not least of these is to apply a linear Interpolation to manifest scores when we have no idea of the distance between them. Even so, journal editors are prepared to accept this measurement gibberish. After all, it is only for 'approximate information' not for testing hypotheses. As Tennant et al point out in their contribution to a special section in the ISPOR house journal *Value in Health* (2004): *As long as primitive counts and raw scores are routinely mistaken for measures by our colleagues in social, educational and health research, there is no hope of their professional activities ever developing into a reliable useful science* [18].

From Imaginary to Real World Claims

After constructing its simulated evidence report, ICER, apparently, is proposing to extend its reach to encompass real world evidence. While believing imaginary claims should precede real world evidence may seem strange, but there is no conflict. This is because the ICER imaginary reference case value claims are not intended and never were intended to support credible, evaluable and replicable hypotheses. It is impossible to contradict them. There is the option, of course to use real world evidence to 'modify' assumptions, but that allows ICER to propose another imaginary world to generate a further set of non-evaluable claims.

If ICER is to be taken seriously, as a valued contributor to health technology assessment, then it needs to abandon the reference case value assessment framework and the absurd incremental cost-per-QALY fantasy. Even if ICER proposed cost-per-QALY hypotheses, these would be rejected because of their reliance on ordinal manifest scores. If ICER wished to make contribution to QoL claims, it should abandon the EQ-5D and other instruments that failed to meet RMT standards. Instead, and this is extremely unlikely, it could act as sponsor for a migraine QoL instrument that met RMT standards.

Going Forth

In the case of migraine, indeed in all the evidence reports produced by ICER, manufacturers should not only ask the evidence reports to be withdrawn, but should ensure health system decision makers are kept informed. It is not a question of modifying the ICER imaginary worlds, possibly bringing in Harry Potter, but of putting the ICER VAF framework to one side. ICER is in no position to argue, after its evidence report has been received, that it might consider some aspects of a 'next steps' research program to include, possibly, at some time in the future aspects of the patient voice and consideration of the status of rare disease, and the needs of patients and caregivers.

In migraine, the unfortunate fact is that, without understanding the nonsense of the ICER imaginary worlds, media representatives and health system decision makers take the ICER recommendations at face value. It is as if they made formulary decisions based on the daily horoscope for their birth sign. It is all pseudoscience. The ICER model, with its bizarre cost-per-QALY claims is an unnecessary distraction. It short circuits rational, evidence based discussions in formulary decision making; discussions which could point to the role of needs-based patient centric instrumentation to assess claims for target migraine groups, revised protocols for ongoing clinical and observational studies and, overall, a commitment to the discovery of new facts.

Science does not advance through the fabrication of imaginary worlds built on assumptions, real or imagined. This is echoed by Newton (Isaac Newton 1642-1727) with Descartes as his target (René Descartes 1596-1650) in saying '*hypotheses non fingo*' (I do not feign hypotheses). Descartes in Newton's view had 'produced fantastic and untestable ideas, then assumed them to be true and used them as building blocks of his philosophy ' [19].

If we are to understand the contribution of therapies in migraine, this does not occur through the fabrication of imaginary cost-per-QALY claims. The denial of patient access through modeled imaginary worlds which, absent deconstruction of the ICER VAF, health care decision makers take at face value, is a travesty. The ICER VAF for migraine, as a model built entirely from assumptions, is an obstacle to discovery. This is, as noted in previous commentaries, nonsensical. If a new product or device is to be admitted to formulary and a price negotiated, we don't need fabricated imaginary value claims, but credible evidence for the impact of the product on a target treating population. At launch, we may only have clinical data. This may be sufficient to propose cost-outcome claims, but these must be credible, evaluable and replicable. If these data points are not to hand then, rather than creating an imaginary modeled world, the focus should be on claims assessment and feedback to a formulary committee. Not, it must be emphasized, a retreat to a medieval world where the search for new facts is discouraged; subsumed in an acceptance of imaginary and unsupported claims for therapy impact and value.

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