

# MAIMON WORKING PAPERS

## Working Paper No. 1 February 2020

### More Unnecessary Imaginary Worlds: Cystic Fibrosis and the Institute for Clinical and Economic Review's Draft Evidence Report

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#### Abstract

*On 20 February 2020, the Institute for Clinical and Economic Review (ICER) released its draft evidence report to establish the value of innovative therapies in the treatment of cystic fibrosis. Following its usual practice, ICER contracted with an outside group to construct a value assessment framework, in this case a microsimulation model, to generate value claims. The primary outcomes for value claims were incremental cost-per-QALY simulations for four target cystic fibrosis populations. The value assessment, in common with the same model applied earlier by ICER in cystic fibrosis, recommended substantial price discounts based on arbitrary threshold cost-per-QALY values. Unfortunately, the entire exercise, based on as detailed in previous commentaries in INNOVATIONS in Pharmacy is essentially a waste of time. Not only is the reference case model presented by ICER only one of a multiverse of other models, all driven by a selective application of model structure and assumptions, but the fact that the utilities that are applied to hypothetical time spent in different disease stages to modeled QALYs and lifetime cost-per-QALY claims fail to meet fundamental measurement axioms: they are ordinal manifest scores. Applied to target cystic fibrosis target patient groups, the modeled claims are meaningless. From the manufacturer's perspective, in this case Vertex Pharmaceuticals who have developed all the cystic fibrosis therapies 'modeled' by the ICER contractor, their response to ICER claims should be to reject them out of hand; the constructs are imaginary and the outcome claims nonsense.*

*Keywords: imaginary worlds, cystic fibrosis, ICER, pseudoscience, nonsense claims, nonsense recommendations*

#### 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. ICER has issued two evidence reports on cystic fibrosis. The first report, a final evidence report was released in 2018; the second report, a draft evidence report, on 20 February 2020<sup>1</sup><sup>2</sup>. The focus of this commentary is on the second report. Even so, this analysis of the manifest failings of the second report apply equally to the first report: neither the economic model

nor the recommendations for pricing and access should be taken seriously. Indeed, it is worth noting that following the release of the first evidence report Vertex Pharmaceuticals, whose drugs featured in ICER's modeled 'analysis', Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor and ivacaftor), issued a strong condemnation of the ICER methodology, 'a flawed scientific methodology', and a 'sham' evaluation process, where conclusions were agenda-driven and pre-ordained<sup>3</sup>. In the second report it once again is only Vertex cystic fibrosis therapies that are considered. These include the therapies considered for modeling in the first report but with the addition of the Trikafta (elexacaftor/tezacaftor/ivacaftor) combination.

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The ICER model for the 2020 draft evidence report was an updated version of their previous imaginary microsimulation model. The modeling objective was to estimate the hypothetical lifetime effectiveness and cost-effectiveness of CFTR modulator treatments plus best supportive care for cystic fibrosis patients in the specific imaginary model framework. The primary health outcome was quality adjusted life years (QALYs) utilizing EQ-5D-3l utilities. Other lifetime horizons outcomes were life years, equal value of life years gained and lifetime number of acute pulmonary exacerbations. There was no expectation that any of these fabricated outcomes could be evaluated empirically given the

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lifetime framework. These imaginary outcomes were discounted, along with costs, in the base case model at 3%.

The lifetime microsimulation model created an imaginary value assessment for four possible therapeutic options for four cystic fibrosis populations: (i) patients who are candidates for Kalydeco monotherapy; (ii) patients who are homozygous for the F508del mutation; (iii) patients who are heterozygous for the F508del mutation; and (iv) patients who are heterozygous with minimal function mutation. The primary model variable was ppFEV<sub>1</sub>, modeled as a continuous variable to capture the effect of the CFTR modulator drugs. Imaginary patients in the model are simulated to accumulate life years, QALYs and costs. EQ-5D ordinal utility values were assigned to ppFEV<sub>i</sub> status to generate QALYs per year and cumulate them over the lifetime of the patient.

The base case incremental cost-per-QALY ‘results’ (against best supportive care) for each of the patient models are, of course, imaginary and not for empirical assessment (i.e., hypothesis testing). We have to take them at face value; or reject them accordingly. For each population simulated estimates are presented for total QALYs, total life years and equal value life years. Imaginary QALY gains are modest, ranging from 4 to 7 years. Incremental simulated lifetime costs are substantial ranging from \$5.5 million to \$7.0 million dollars, set against best supportive care. Consequent estimates of imaginary cost-per-QALY gained are, unsurprisingly, substantial. These range from \$818,000 for Trikafta plus best supportive care to \$1,060,000 Kalydeco plus best supportive care and Symdeko plus best supportive care. Inevitably, these lead ICER to conclude that while the therapies clearly have substantial clinical benefits (which we knew anyway), this can only be realized if there are substantial price discounts. According to the imaginary microsimulation, a discount of 35 – 51% would be necessary to reach a cost-effectiveness threshold of \$500,000/QALY for Kalydeco and Symdeko (as they classify as a rare disease target) while discounts of 65 – 66% would be necessary for Trikafta to reach a cost-effectiveness threshold of \$200,000/QALY. Again, caution is in order as these are entirely assumption driven imaginary claims; alternative models could lead to quite different imaginary conclusions.

### Nonsense on Stilts

A recent commentary in INNOVATIONS in PHARMACY reviewed the latest ICER VAF to be applied over the period 2020 to 2023<sup>4</sup>. 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<sup>5</sup>.

If they apply 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 cystic fibrosis, 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 cystic fibrosis. 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)<sup>6</sup>.

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 cystic fibrosis 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 cystic fibrosis, 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<sup>7</sup>. 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

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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-evaluative 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 17<sup>th</sup> 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) <sup>8</sup>.

By the early 20<sup>th</sup> 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' <sup>9 10</sup>. 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. This leads to the obvious point that claims or models should not be judged on the realism or reasonableness of assumptions or on whether the model 'represents' for a public advocacy research group such as ICER their perception of a future, yet unknown, reality.

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 <sup>11</sup>. 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 cystic fibrosis model of the therapies offered by Vertex Pharmaceuticals, 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. 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*' <sup>12</sup>. 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 cystic fibrosis world these are combined to produce QALYs for the modeled life span.

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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 could equally well be labeled and ranked (ordinally) as A, B, C, D etc. 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. 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, then it must be rejected. In the case of cystic fibrosis, ICER and its contracted model group must be able to demonstrate Rasch measurement properties for each patient group modeled with EQ-5D scores. Absent such an assessment for unidimensionality and interval properties, the model for each cystic fibrosis group collapses. QALYs and consequent incremental cost-per-QALY claims have no meaning.

### 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, yet ordinal, utilities. Adopting a QoL instrument with interval scoring properties would negate this business model. Indeed with a disease specific QoL index, QALYs could be abandoned. We would have an instrument that meets fundamental RMT standards.

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 this may bear no relation at all as to whether the needs of the patient are being met.

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<sup>13</sup>. 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<sup>14</sup>. We have an armory of these instruments specific to disease states suitable for assessing therapy response. Imaginary QALYs are not required.

### HRQoL in Cystic Fibrosis

ICER's insistence on creating imaginary cost-per-QALY worlds for pronouncements on pricing in cystic fibrosis is clearly nonsense. It is not a question of the ICER model being only one of many alternative models, which it is, but through its denial of the patient voice; putting needs based instruments to one side in its insistence on an operational symptom/response measure (one of many generic alternatives) to drive its outcomes.

This does not mean that ICER is not aware of disease specific instruments in cystic fibrosis. Reference is made to probably the most widely used instrument, the Cystic Fibrosis Questionnaire (CFQ)<sup>15</sup>. In the revised version (CFQ-R) there are three versions: adolescents and adults, children and parents. The instrument, adolescent and adult version, has 44 items on 12 generic and disease specific scales with a composite single score (0 – 100 scale).

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Unfortunately, while the CTQ meets classical test theory criteria, it does not exhibit interval scaling properties and does not consider a broader QoL needs framework in instrument development. The scale only captures manifest scores. Once again, we find an instrument that is widely used but where those using it are not aware of its lack of fundamental measurement properties. This criticism applies across the board to the majority of patient recorded outcome (PRO) instruments. Unless there has been a review of Rasch standards with possible recalibration, including exclusion, of items, then a PRO instrument must be assumed not to meet RMT standards.

### Creating Ordinal Utilities

The basis for the ICER imaginary QALY creation is a study by Schector et al which 'creates' utility scores for health states defined by FEV<sub>1</sub>%<sup>16</sup>. The basis for this exercise is a study by Bradley et al which reported for a UK cystic fibrosis population<sup>17</sup>. This study produced three EQ-5D scores corresponding to: (i) 0.85 no current pulmonary events ; (ii) 0.79 mild (no hospitalizations) pulmonary exacerbation; and (iii) 0.60 severe (hospitalization) pulmonary exacerbations. Apparently these correlate well with the ordinal scores of the CTQ. Once again, these EQ-5D-3L 'scores' lack interval measurement properties; we can only rank them as the difference between the 'scores' has no meaning.

Remember, any EQ5D 'utility' is a an ordinal manifest score. The only arithmetic operations we can undertake are to give modal or median measures; addition, subtraction and multiplication and division are impossible as the scales fails to have interval, or for the latter two operations, ratio properties (i.e., the ratio scale requires a 'true zero').

Nevertheless, in defiance of the axioms of fundamental measurement, in a successor study Tappenden et al translated the Bradley et al results and generated estimates of EQ-5D based on FEV<sub>1</sub>%. FEV<sub>1</sub> > 70% EQ-5D = 0.864; FEV<sub>1</sub>% 40 – 79% = EQ-5D 0.810; and FEV<sub>1</sub>% < 40 = EQ-5D 0.641<sup>18</sup>. Despite the fact that these EQ-5D 'estimates' are still manifest scores, Schector et al went one step further and undertook a linear interpolation to 'predict' EQ-5D manifest scores for nine FEV<sub>1</sub>% intervals. These scores were used to populate the ICER cystic fibrosis model and create imaginary QALYs. Nonsense begets nonsense.

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*<sup>19</sup>.

### 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 cystic fibrosis 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 17<sup>th</sup> 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 (e.g., announcing the Parousia in drug evaluations) we have no idea what 'approximate' means.

The cystic fibrosis 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 cystic fibrosis 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 cystic fibrosis.

### Going Forth

In the case of cystic fibrosis, indeed in all the evidence reports produced by ICER, manufacturers should not only ask the



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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 cystic fibrosis, 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 if they made formulary decisions based on the daily horoscope for their birth sign. It is all pseudoscience. Certainly, products in cystic fibrosis are considered expensive, but this has not stopped manufacturers such as Vertex from entering into market access programs. 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 cystic fibrosis 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' <sup>20</sup>.

If we are to understand the contribution of therapies in cystic fibrosis, 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 cystic fibrosis, 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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