MAIMON WORKING PAPERS **www.Maimonresearch.net**

MAIMON WORKING PAPER No. 22 OCTOBER 2020

MORE COVID-19 NONSENSE: THE ICER MODELLED THRESHOLD PRICE BENCHMARKS FOR REMDESIVIR

Paul C Langley Ph.D., Adjunct Professor, College of Pharmacy, University of Minnesota

Abstract

ICER's persistence with the creation of impossible or I-QALY based imaginary lifetime simulations to support, with cost per I-QALY thresholds, 'fair' pricing and access recommendations, while not admired, is worth our attention. Indeed, ICER is a necessary provocateur. The continued publication of reference reports with their reference case simulations provide a necessary and continuing target for informing manufacturers and health decision makers of ICERs manifest limitations. On October 9, 2020 ICER released a statement informing those who believe in imaginary worlds that they are being elevated to a cloud-based imaginary interactive modeler platform. This 'initiative' is intended to enhance the transparency of ICER's imaginary simulations and allow access to all ICER lifetime simulations. The first model proposed is for Covid-19 to assess the imaginary cost-effectiveness of Remdesivir and other treatments for Covid-19.This is, according to ICER, a 'landmark international program' for health technology assessment agencies around the world who are committed to the construction of nonsensical I-QALY imaginary lifetime simulated and non-evaluable claims for product pricing and access. The purpose of this note is to re-emphasize the impossible nature of the ICER reference case modeling, landmark or otherwise, irrespective of whether it is cloud based or restricted to terra firma.

INTRODUCTION: THE CLOUD CAPPED TOWERS[1]

ICER's belief that it is making a significant contribution to the pricing of Remdesivir in hospitalized patients with COVID-19 should not be taken seriously [2]. It has been recognized for some years that the ICER approach to making claims for cost-effectiveness and fair or threshold pricing for products is fatally flawed [3]. Not only does the ICER methodology fail the standards or normal science, but more egregiously the model fails to recognize the limitations imposed by the axioms of fundamental measurement [4].

ICER's perseverance with its commitment to a pseudoscience is understandable: its reference modeling business case rests on the assumption that utility scales have ratio properties and that the creation of imaginary cost-effectiveness I-QALY claims is universally accepted. ICER's continuing belief that utility scales (in particular the EQ-5D-3L) have ratio properties (yet a ratio scale without a true zero) is demonstrated in its 'landmark international program', led by its customizable imaginary interactive Covid-19 cost-effectiveness model [5]. This program is intended to promote health technology assessment through the manipulation of the impossible ICER imaginary simulations to a new level on the global

stage. The Covid-19 model, if indicative of the proposed interactive imaginary modeler platform suffers from ICER's mistaken belief in the ratio properties of ratio scales [6]. Even before launch, the platform is fatally flawed. Health technology assessment agencies should be advised to ignore claims for cost-effectiveness and fair pricing produced by this type of model. The proposed platform may be a landmark for health technology assessment and, hopefully, eagerly embraced by the technology assessment community; but for the wrong reasons.

REJECTING THE ICER REMDESIVIR INTERACTIVE MODEL

There is no excuse to ignore the axioms of fundamental measurement. The physical science and mainstream social science (e.g., economics) have long recognized that any instrument to measure outcomes, response to therapy, should conform to these axioms, to include dimensional homogeneity where instruments measure specific attributes. Indeed, the axioms should be recognized from the first stages in instrument development. Unfortunately, one of the more intriguing features of health technology assessment is the insistence that the axioms can be ignored, or more accurately were never recognized or understood, so that health technology assessment (epitomized by the ICER reference case) rests on the construction of pseudoscientific or approximate evidence from imaginary lifetime simulations [7]. Hypothesis testing is firmly rejected.

For technology assessment and claims, and the Covid-19 model is an excellent exemplar, practitioners need to believe that utility scales have ratio properties (although there is some confusion in the literature over the interpretation of interval as opposed to ratio scales). If a scale is to exhibit ratio properties it must not only have interval properties (by default) where distance is invariant, but a true zero. This is critical: the scale must not be capable of creating negative values. This is violated in the case of multiattribute utility scales. The algorithm that creates EQ-5D-3L utilities can generate negative values; euphemistically labelled as 'states worse than death' with the implications for fundamental measurement ignored. In fact these utility scores are ordinal scales. ICER has been asked if it can prove that the utility scores are on ratio scale; the response was 'it had an understanding' but could not provide a proof. An ordinal scale, where the distance between scores is unknown, can only support modes, medians and non-parametric statistics. Ordinal scales cannot support the usual arithmetic operations of addition, subtraction, multiplication and division.

The implications are interesting: as you cannot multiply time spent in a disease state or post-disease recovery by an ordinal score, the construction of lifetime quality adjusted life years is a mathematical impossibility. The QALY is an impossible creation. In the case of the modelled claims for Remdesivir the construction of QALYs (now called I-QALYS or impossible QALYs) is nonsensical [8]. A recent PubMed search on the term QALY yielded 18,972 hits since 1981. None have apparently realized the QALY is an impossible construct. Lifetime post-recovery Remdesivir modelled QALY claims produced by ICER are meaningless.

Apart from the I-QALY, the ICER model, as has been pointed out on numerous occasions, fails the evidentiary standards of normal science. Claims stretching decades into the future, driven by a mix of

clinical results and assumptions, fail the demarcation test between science and pseudoscience (e.g., natural selection vs. intelligent design) for the simple reason that the ICER claims for therapy response lack credibility and are neither empirically evaluable nor replicable [9]. This is a further reason for rejecting the Remdesivir modeling.

I-QALY THRESHOLDS FOR PRICING REMDESIVIR

The application of cost-per-QALY thresholds to establish pricing benchmarks for Remdesivir is, of course, a further wasted effort. If the I-QALY is an 'impossible' construct then the cost-per-I-QALY threshold is similarly impossible. The ICER imaginary Covid-19 model for Remdesivir proposes three cost-per-I-QALY thresholds: $50,000 per I-QALY, $100,000 per I-QALY and $150,000 per I-QALY. Apart from the fact that these are imaginary metrics, if the I-QALY is an impossible mathematical construct attaching a price to it seems somewhat absurd. In any event, the ICER Covid-19 model base case with an assumed mortality benefit creates imaginary cost-per QALY pricing for a course of treatment of $4,580, $18,640 and $32,700 respectively for the three thresholds. ICER then proposes that the relevant pricing estimate should be related to the $50,000 per QALY thresholds as the most policy relevant (i.e., the cheapest). If there is no mortality benefit then the price declines to $310, $620 and $930 respectively.

The concern the manufacturer (and observers) must have is that government agencies and health plans will take these figures seriously. Indeed, ICER points to situations where the model has informed reimbursement recommendations for Remdesivir. In the media release (9 October 2020) two applications are noted: the Quebec Institut national d'excellence en santé et en services sociaux (INESS) and the MOSAIC modelling group in South Africa. This is unfortunate but they are not alone given the role reference case imaginary I-QALY worlds play in formulary decisions in single payer health systems. The most influential player here is the National Institute for Health and Care Excellence (NICE) in the UK [10].

CONCLUSION: AFTER THE BASELESS FABRIC OF THIS VISION[1]

Pricing negotiations should not be driven by, or even associated with, imaginary lifetime simulations which not only defy the standards of normal science but are based upon the unwarranted belief in the ratio properties of utilities to create I-QALYs. Not only are claims for incremental lifetime cost-per-QALYs nonsensical, but so is the application of cost per I-QALY thresholds. Covid-19 is too serious a pandemic for the pricing and targeting of Remdesivir to be driven by interactive models which rest on ignorance of the standards of fundamental measurement. Changing assumptions to propose new 'fair' prices if and when more data become available is simply a waste of time.

Peer reviewed clinical response data for Remdesivir are in short supply. The latest peer reviewed paper points to a limited application of the drug to hospitalized patients requiring any supplemental oxygen [11]. It is only in this group that Remdesivir is claimed to be statistically superior to placebo. In less severe and more severe groups the results point to no significant response difference. Pricing and access negotiation must be driven by data that meets required measurement standards. At the moment

negotiations are not helped by impossible approximate information modelled claims for a 'fair' price; where we don't know whether it is right, if it is wrong and we will never know. Indeed, we were never expected to know.

We should get back to basics and negotiate a provisional price on the evidence to hand. One obvious approach is outcomes-based value contracting. Establish therapy targets, provide protocols for their assessment with a negotiated base provisional price. This is not rocket science; we don't need baseless visions. We have ample experience with alternative forms of evidence-driven value contracting. Pricing is provisional, subject to claims assessment feedback. Covid-19 and the promise of Remdesivir should not be short-changed by a pricing model that defies the standards of normal science with false claims for its measurement properties and the discredited I-QALY.

REFERENCES

[1] Shakespeare, W. *The Tempest*. Act 4, Scene 1. Wells S, Taylor G (Eds). The Oxford Shakespeare (2nd Ed.) Oxford: The Clarendon Press, 2005

[2] Institute for Clinical and Economic Review (ICER). Alternative Pricing Models for Remdesivir and other potential treatments for COVID-19. Boston June 24,2020, https://icer-review.org/wp-content/uploads/2020/06/ICER-COVID_Revised_Report_20200624.pdf

[3] Langley PC. Nonsense on Stilts Part 1: The ICER 20209-2023 Value assessment Framework for Constructing Imaginary Worlds. *InovPharm*. 2020;11(1).No. 12 https://pubs.lib.umn.edu/index.php/innovations/article/view/2444

[4] Langley PC and McKenna SP. Measurement, modeling and QALYs [version 1) F1000Research 2020, 9:1048 https://doi.org/10.12688/f1000research.25039.1

[5] Institute for Clinical and Economic Review. Media release: Landmark International Program. 9 October 2020 https://icer-review.org/announcements/international-hta-agencies-use-icer-covid-model/

[6] Langley P. The Impossible QALY and the Denial of Fundamental Measurement: Rejecting the University of Washington Value Assessment of Targeted Immune Modulators (TIMS) in Ulcerative Colitis for the Institute for Clinical and Economic Review (ICER). *InovPharm*.2020;11(2): No 17 https://pubs.lib.umn.edu/index.php/innovations/article/view/3330/2533

[7] Neumann P, Willke R, Garrison L. A health economics approach to US value assessment frameworks –Introduction: An ISPOR Special Task Force Report (1). *Value Health*. 2018;21:119-25

[8] Langley P. The Great I-QALY Disaster. *Inov Pharm*. 2020;11(3): No 7
https://pubs.lib.umn.edu/index.php/innovations/article/view/3359/2517

[9] Piglucci M. Nonsense on Stilts: How to tell science from bunk. Chicago: University of Chicago Press, 2010

[10] Langley P. Sunlit uplands: the genius of the NICE reference case. Inov Pharm. 2016;7(2): Article 12 https://pubs.lib.umn.edu/index.php/innovations/article/view/435

[11] Beigel J, Tomasek K, Dodd L et al. Remdesivir for the treatment of Covid-19 – Final Report. *NEJM*. 8 October 2020
https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764