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MAPPING IMPOSSIBLE UTILITIES: THE ICER REPORT ON TEZEPelumAB FOR SEVERE ASTHMA (REVISED)

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Abstract

The focus of this commentary is on the attempt to create EQ-5D-3L ordinal preferences from a disease specific asthma questionnaire, the Asthma Quality of Life Questionnaire (AQLQ). The question is whether it is possible from the perspective of fundamental measurement to create a simple linear algorithm to map AQLQ scores to EQ-5D-3L preferences. It is proposed that this is mathematically impossible as the aggregate AQLQ score is ordinal, apart from the fact that the AQLQ is a multiattribute score that lacks construct validity and any pretense to having interval properties. Disallowing the mapped utilities means that the modelling cannot be sustained. It is proposed that the focus should be on single attribute measures of the latent construct “need fulfillment quality of life”. These measures would meet the required standards of Rasch Measurement Theory (RMT) applying simultaneous conjoint standards of measurement theory, as well as capturing the patient voice.

Keywords: ICER, tezepelumab, modeling, pricing, asthma, Rasch Measurement Theory

INTRODUCTION

The release on 4 November 2021 of the final evidence report by the Institute for Clinical and Economic Review (ICER) for tezepelumab (Tezspire; Amgen and Astra Zeneca) in severe asthma is critically examined in this commentary regarding the creation of imaginary evidence for cost-effectiveness and the consequent recommendations for a social Health Benefit Price Benchmark (HBPB)¹. As detailed in previous commentaries and in submissions to ICER on previous evidence reports, the ICER reference case requirements for modelled comparative claims fail the standards for normal science^{2 3 4}. Assumption driven simulation models produce just one of a potential multitude of tezepelumab models; none can claim superiority over the other in choice of assumption because claims from the past cannot support claims on an unknown future. Add to this the fact that the application of generic multiattribute scores to create a quality adjusted life year (QALY) is mathematically impossible and you are left with value claims that are impossible to empirically evaluate or replicate⁵.

THE TEZEPelumAB IMAGINARY MODEL

Tezepelumab is a monoclonal antibody that targets thymic stromal lymphopoietin (TSLP), in severe asthma. It is administered by subcutaneous injection every 4 weeks. It is presently designated a breakthrough therapy with approval expected from the FDA in quarter 1, 2022. Its price has yet to be determined but the assumption driven simulation model assigned a placeholder annual net price of \$28,000 (based on the price of dupilumab) for making an initial pricing recommendation.

The model involves a lifetime Markov framework where a hypothetical asthma population proceeds through two recurring health states: an asthma non-exacerbation state and an asthma exacerbation

state. The final absorbing state was death (it cannot recur). Assumption driven estimates of time spent in each health state are multiplied by the ordinal preference or utility score to create impossible QALYs. In this model, as detailed below, the 'preferences' are created by a mathematically impossible 'mapping' from the Asthma Quality of Life Questionnaire (AQLQ) ordinal scores.

The model then proceeds to generate lifetime imaginary QALYs and lifetime imaginary costs. The term imaginary is used because these QALY and cost estimates, as they are by assumption and for the future, are just one of a multitude of possible alternative assumptions to create imaginary claims. Assumptions as to an unknown future cannot be justified by past observations; the problem of induction. For the base case imaginary modeling of tezepelumab plus standard of care versus standard of care yields, respectively, precise yet imaginary \$697,000 lifetime costs and \$228,000 lifetime costs respectively; the corresponding imaginary lifetime QALYs are 15.00 years and 13.91 years respectively or \$430,000 per incremental QALY gained; the base case imaginary value claim.

Applying the impossible imaginary cost per imaginary QALY threshold criteria, the annual price of tezepelumab required to reach thresholds between \$50,000 and \$200,000 per QALY range from \$6,200 to \$15,000 per annum. ICER proposes a socially acceptable imaginary (HBPB) price for tezepelumab between \$9,000 and \$12,000. Validation can be claimed equally for any other model and would be equally unconvincing given the nature of assumption driven simulations and the impossible QALY. The only accepted validation criterion is empirical evaluation of the claims made. If there is no possibility of this, the model should be discarded for decision-making.

A DIGRESSION ON MEASUREMENT

Accurate measurement is the key to value claims that are credible, evaluable and replicable; if measurement fails to meet required standards then the value claim fails. The often quoted statement by Lord Kelvin (William Thomson 1824-1907) is the touchstone: *If you cannot measure, your knowledge is meager and unsatisfactory*⁶. Value claims for comparative response to therapy required in health technology assessment can only survive if they respect the axioms of fundamental measurement^{7 8}.

Following the formalization by Stevens and others in the 1930s and 1940s, scales or levels of evidence used in statistical analyses are classified as nominal, ordinal, interval or ratio⁹. Each scale has one or more of the following properties: (i) identity where each value has a unique meaning (nominal scale); (ii) magnitude where values on the scale have an ordered relationship with each other but the distance between each is unknown (ordinal scale); (iii) invariance of comparison where scale units are equal in an ordered relationship with an arbitrary zero (interval scale) and (iv) a true zero (or a universal constant) where no value on the scale can take negative scores (ratio scale). The implications for the ability to utilize a scale to support use of arithmetic operations (and parametric statistical analysis) are clear. Nominal and ordinal scales do not support any mathematical operations; only nonparametric statistics. Interval scales can support addition and subtraction while ratio scales support the additional operations of multiplication and division as they have a true zero. This zero point characteristic means it is meaningful to say the one object is twice as long as another. To measure any object on a ratio scale it has to be demonstrated that all criteria

for an interval scale have been met with a true zero. It is impossible to take an ordinal score and translate that to a ratio score via a simple linear transformation. If a ratio scale requirement is dictated by the need to create QALYs then that has to be designed from the get-go in instrument development¹⁰. Unfortunately, creating ratio measures for latent constructs is far from settled.

It cannot be assumed, *ex post facto*, that a given scale has interval, invariance of comparison, or ratio properties. This point is made Bond and Cox¹⁰ in their discussion of Rasch Measurement Theory (RMT) theory and its contribution to fundamental measurement: in traditional test theory (TST) and item response theory (IRT) the observed data have primacy; results are exploratory and descriptive of those data. Rasch models are, on the other hand, confirmatory and predictive; a confirmatory model requires the data to fit the model where following the principles of conjoint measurement are sufficiently realized to claim the results are a measurement scale with interval measurement properties¹⁰.

THE ASTHMA QUALITY OF LIFE QUESTIONNAIRE

Although widely used over the past 25 years and useful for addressing certain questions, the AQLQ fails to meet the standards of fundamental measurement; it is a multiattribute ordinal scale. If an instrument to support multiplication is required then it must be dimensionally homogeneous or unidimensional, with construct validity and ratio properties¹¹. The AQLQ score cannot be used to support claims for response to therapy^{12 13 14}. It also ignores the seminal contributions of Rasch, and Luce and Tukey to fundamental interval measurement for detecting measurement structures in non-physical attributes^{15 16}.

Consider how the AQLQ is assembled and the measurement implications of Likert scales¹⁷. This is a 32 item-questionnaire used to assess the physical, occupational, emotional and social qualities of adults 17 to 70 years exhibiting mild to moderate asthma. It is a multiattribute instrument with four domains: symptoms (12 items), activity limitation (6 generic and 5 patient-specific items), emotional function (5 items), and environmental stimuli (4 items). Each item response is on a 7 point Likert scale with responses ranging from 1 = maximal impairment to 7 = minimal impairment. The items are in the form of questions with each of the scale points anchored on a word or phrase and not just the extreme values; descriptors include “totally”, “extremely”, “very”, “moderate”, “some” “a little”. As Wilson et al note: some of these scales may be confusing to respondents as they mix adjectives with other grammatical elements and that there is no published evidence that the anchor words and phrases can be consistently ordered independently of their numerical positioning on the response scale or that the relative positions of different phrases represent approximately equal psychometric intervals¹⁸. The fact that the AQLQ has shown strong classical measurement properties based on integer ratio assumptions, is irrelevant; this only occurs if you ignore the axioms of fundamental measurement and assume the AQLQ has interval properties for the Likert scores (which could equally well be designed on a 7 point scale as $A > B > C > D > E > F > G$ rather than with a numeric assignment $1 > 2 > 3 > 4 > 5 > 6 > 7 > 8$ or even an emoji for each Likert space). In other words, if traditional or classical statistical operations are to be attempted with an instrument such as the AQLQ, then the developers need to demonstrate: (i) that all items are of equal difficulty and (ii) that the spaces between each Likert item are of equal distance¹².

Likert scales do not have interval properties (i.e. invariance of comparisons) between adjacent spaces. Just as we cannot interpret the 'numerical' or 'response' distance between A and B, we cannot interpret the distance between 1 and 2. The easy way out is to ignore the question of the failure to address invariance of comparisons and just assume they exist. In other words, each Likert scale is on a ratio scale because we need to claim after addition of the scores for each individual Likert scale that the overall scale has ratio properties together with the scales for the 4 domains.

As Likert scales are ordinal scales this means the AQLQ combines 32 Likert scales none of which, if we follow the axioms of fundamental measurement, can support averages as the spaces between the integers or letters are unknown. At best, ordinal scales can only support medians and modes and non-parametric statistics. As noted, an ordinal score, unless you assume otherwise, cannot support the arithmetic operations of addition, subtraction, multiplication or division. Nevertheless, the scoring of the AQLQ ignores these requirements of fundamental measurement and treats the scales as if they had interval properties. This allows an average score to be created for each ordinal Likert scale with domain and aggregate scores created by merging the average Likert values for each for each item.

To describe the average AQLQ score as a 'score' is a misnomer; it is a value that results from illegitimate manipulations of Likert scales to produce a 'number' that is meaningless in response to therapy terms. Put simply, you cannot take an integer value from one sub-domain of a Likert scale and add it to another Likert scale. The AQLQ cannot support claims for response to therapy, either as an overall or a subdomain ordinal score. This does not mean the rejection of statistical techniques but the assurance that we are dealing with correct interval measures before application.

THE IMPOSSIBLE ALGORITHM

Mapping from the AQLQ to the EQ-5D-3L is accomplished by application of the following algorithm for each respondent where AQLQ is the aggregate (annual) score ¹⁹:

$$\text{EQ-5D-3L} = 0.14 + 0.12 \text{ AQLQ}$$

The first point to note is that the AQLQ as an ordinal or ranked score cannot support multiplication; the mapping falls at the first hurdle. Certainly there are integer values but these fail to have interval let alone ratio properties. Aggregating over Likert-based integer scores (which is itself invalid) yields an AQLQ ordinal score. This is captured in the algorithm to create the EQ-5D-3L score (somewhere in the range 0, = death and 1 = perfect health. There is an issue: Is this transformation (which is invalid) intended to create ordinal scores? There is no mysterious alchemy that allows an ordinal score to be translated by a single algorithm to a ratio EQ-5D-3L; it is an impossible score. A failure which characterizes later efforts at mapping from the AQHQ ^{20 21}.

It is worth noting that similar issues are faced in trying to map from aggregate scores created by the St George's Respiratory Questionnaire (SGRQ) to EQ-5D-3L preferences in COPD studies ²². Again, we face the issue of ordinal scores (the aggregate SGRP score) being applied to create, presumably, ordinal

scores; again a mathematical impossibility, where the 'aggregate' SGRQ score is an unorganized set of integers attached to polytomous and binary responses. Again, where the SGRQ and EQ-5D-3L are included in the same study as ordinal scores, it is easy to map (ignoring measurement theory) individual responses from one to the other but this assumes that the two are ratio and not ordinal scores for the respondents. As it stands, they are both ordinal scores so that mapping is mathematically impossible. Whatever transformations are attempted the AQLQ and the SGRO will never support a ratio transformation as the output data are only on an ordinal score. Given that the EQ-5D-3L/5L instruments support only ordinal scores, it seems odd to pursue creating ordinal scores through mapping, if it is to be believed, from one ordinal score (the AQLQ) to another (EQ-5D-3L) unless, of course, one believes that both instruments are ratio scores without any necessity of proof. The problem is that you cannot believe, on the one hand, that in mapping we are creating a ratio score (from an ordinal score?) while on the other hand, direct algorithmic measures of the EQ-5D-3L/5L have negative values and fail the standard for a ratio score. The utilities which are assumed by application of the mapping algorithm to have ratio properties are only ordinal scores. The mapped impossible ordinal preferences cannot support the creation of QALYs.

NEXT GENERATION QUALITY OF LIFE VALUE CLAIMS

If quality of life is an appropriate attribute to capture response to therapy, then the focus should not be on health related quality of life (HRQoL) defined by a short-list of symptoms or attributes that are bundled together to create a dimensionally heterogeneous, multidimensional score that lacks construct validity, but rather single attribute measures of the latent construct "need fulfillment quality of life". These measures meet the required standards of Rasch Measurement Theory (RMT) applying simultaneous conjoint standards of measurement theory, as well as capturing the patient voice²³. In the case of asthma we have the Asthma Life Impact Scale (ALIS) that was developed some fifteen years ago²⁴. The rationale for the ALIS is that the focus of patient reported outcomes measures in asthma, such as the AQLQ, should not be exclusively on symptoms and functioning (which should be captured as separate unidimensional attributes), Rather we require a holistic, single latent construct approach, with the question: to what extent are the needs of asthma patient's being met under various therapy intervention regimens. In other words, what is the overall impact of a therapy on the patient's quality of life; the conceptual framework is that quality of life is dependent on an individual's ability to fulfill fundamental needs and that their quality of life is high when these needs are met. With the application of RMT, the instrument items are selected to reflect a single underlying unidimensional construct with face and content validity, with overall construct validity. Scores on the final version of ALIS range from 0 to 22 with a high score indicating a major negative impact of asthma where each item elicits a binary response of True/Not true to create an interval scale. This allows for value claims regarding interval response to therapy, but not a ratio scale.

Importantly, more recently a transformation algorithm has been developed to translate disease specific interval measures such as ALIS into bounded ratio measure in the range 0 to 1²⁵. This

gives, for the first time, a coherent disease specific unidimensional measure of quality of life that evaluates the extent to which need is fulfilled and the response to therapy options in disease specific quality of life terms. We are now in a position to abandon instruments such as the AQLQ and the ordinal EQ-5D-3L/5L preferences (including the applications of impossible mapping algorithms to create one ordinal scale from another) in favor of instruments to capture quality of life which meet required fundamental measurement standards that could be applied in evaluations²⁶.

CONCLUSIONS

Many will find it difficult to accept the fact that the current focus in health technology assessment on creating evidence through assumption driven simulations not only defies the standards of normal science but the axioms of fundamental evidence. In this respect, it is worth noting some anonymous reviewer comments received in the peer-review process for this commentary. Reviewer 1 viewed this commentary as *'a cogent analysis of the transformational fallacies associated with quality of life measurements that violate the axioms of fundamental statistical science'*. Adding *'mathematical methods used by the Institute for Clinical and Economic Review are not only simplistic, but invalid, because ordinal scales cannot be transformed using an aggregate linear algorithm'*. The reviewer further stated that the commentary provides *'a timely counter argument ... against pharmacoeconomic pseudo-science masquerading as evidence-based public policy'*. Reviewer 2 echoed these concerns as an important commentary noting that *'The manuscript focuses on leading edge, novel ideas for improving, modernizing, and advancing pharmacy practice, education and/or policy'*.

Based on the evidence presented in this commentary, it is proposed that a fresh focus should be on single attribute measures of the latent construct "need fulfillment quality of life". These measures would meet the required standards of Rasch Measurement Theory (RMT) applying simultaneous conjoint standards of measurement theory, as well as authentically capturing the patient voice.

Note: The opinions expressed in this paper are those of the author.

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