RASCH MEASUREMENT AND PATIENT REPORTED VALUE CLAIMS: A PRIMER FOR HEMOPHILIA

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

ABSTRACT

A commitment to the standards of normal science, including fundamental measurement and specifically Rasch Measurement Theory (RMT) are essential prerequisites in assessments of therapy response in hemophilia A and B, as they are in other disease states of target patient populations. The assessment and value claims for therapy response in hemophilia fail at two levels. First, from the creation of assumption driven hemophilia modeled lifetime or long-term simulations built on incremental cost-per-quality adjusted (QALY) constructs; which are mathematically impossible and, second, from the commitment to disease specific outcomes measures in pediatric and adult hemophilia patients which fail RMT standards for single, latent attribute, unidimensional measures for hemophilia quality of life, symptoms, activities and satisfaction with care. The purpose of this commentary is to point out the manifest failings in claims for hemophilia response and to propose a new start in hemophilia studies to identify core claims that meet required measurement standards. This applies to both the development of new patient reported outcome instruments as well as the evaluation of existing instruments, with a focus on polytomous instruments and their sub-domains, to evaluate their possible application as measures that approximate RMT requirements.

Keywords: hemophilia, Rasch measurement, false outcome claims

INTRODUCTION

The release of the latest evidence report from the Institute for Clinical and Economic Review (ICER) for gene therapies in Hemophilia A and B raises a number of critical questions regarding the contribution, if any, of assumption driven models for non-evaluable cost effectiveness claims. The failure of assumption driven cost-per-quality adjusted life year (QALY) simulations, as the centerpiece of the current standard in health technology assessment (HTA), have been made clear in a number of recent publications. The case against modeled claims is that they fail the standards of normal science and, in particular, the standards for fundamental measurement. Unfortunately, rejecting the contribution of assumption driven simulations to support claims for cost-effectiveness and formulary decision making, does not mean that fundamental measurement can be put to one side. The opposite is the case and is exemplified in the attention given in hemophilia A and B over the past 20 years or more to inappropriate multiattribute disease specific measurements developed with scant regard for the standards of normal science and fundamental
measures in evaluating patient outcomes that are credible, evaluable and replicable. If we cannot measure our knowledge is meager (Lord Kelvin).

The purpose of this brief commentary is to make clear that the issue of the standards for fundamental measurement, Rasch Measurement Theory (RMT)\(^5\)\(^6\), has been ignored, not only in hemophilia studies, but more widely in recommendations by groups attempting to achieve a consensus, following most recently with standards endorsed by the International Consortium for Health Outcomes Measurement (ICHOM), for patient relevant or centric outcome measures in hemophilia\(^7\). Three questions are raised: (i) is there any merit to the application of generic multiattribute scores in evaluating respondent status and response to therapy in hemophilia in terms of quality adjusted life years (QALYs); (ii) is it possible to ignore standards for fundamental measurement in proposing patient relevant health outcomes in hemophilia; and (iii) can we set fundamental measurement standards for patient reported outcome measures in hemophilia that capture more adequately the needs of patients and caregivers in hemophilia?

**VALUE CLAIM STANDARDS**

There are three standards that value claims must meet if they are to be accepted by a formulary committee or health system\(^2\). These are:

- All value claims must refer to single attributes that meet the demarcation standards for normal science: they must be credible, evaluable and replicable
- All value claims must be consistent with the limitations imposed by the axioms of fundamental measurement: they must meet interval or ratio standards
- All value claims must be submitted with a protocol detailing how they are to be empirically evaluated

Failure to meet these standards must result in a claim being rejected. Accepting these standards means the end of assumption driven imaginary model simulations and attempts to pass off non-evaluable claims for cost-effectiveness as meaningful decision tools. Insisting on these standards means all claims are consistent with the credibility, evalability and replication standards of normal science, including fundamental measurement, supporting hypothesis testing and progress in our understanding of the merits of hemophilia interventions.

**IMPOSSIBLE UTILITY SCORES AND QALYs**

The emphasis in HTA on preference scores and QALYs is in large part the result of the commitment to incremental simulated cost-per-QALY claims; the rejection of hypothesis testing in favor of approximate information\(^8\). To create the assumption driven simulation model you require a preference score; what is overlooked is that the utility or preference score must have bounded ratio scale properties; that is a true zero, invariance of comparison and capped at unity. None of the existing utility or preference techniques (e.g., standard gamble [SG] or time trade off [TTO] or the EQ-5D-3L/5L, HUI Mk2/3, SF-6D or SF-36 [PCS and MCS components] have this property. They produce, as they are defining or describing limited descriptions of health states, only composite ordinal scores; they lack dimensional homogeneity and construct validity\(^3\). As an
ordinal score they cannot support standard arithmetic operations (addition, subtraction, multiplication, division); only non-parametric operations which exclude claims for mean values and measures of dispersion. At best we can report medians and an interquartile range. As the QALY requires time to be multiplied by a preference score, the QALY is mathematically impossible.

Judged against the required standards for patient outcomes in terms of RMT, we have a long way to go in hemophilia value claims to ensure that patient reported outcomes are being appropriately measured. These utility instruments lack a fundamental requirement of RMT, conjoint simultaneous measurement, where from a patient centric perspective response to therapy needs to take account of both the difficulty of achieving an objective and the ability of the patient (or caregiver) to realize that objective. In Rasch measurement the objective is to create a meaningful measure of a latent construct. An example would be needs fulfillment: what are the needs (in holistic terms) of adults, adolescents and caregivers, with a target group defined by disease severity in hemophilia, given the difficulty of the need and the ability of the respondent to realize that need, how do they respond to competing therapy interventions, including the option of gene therapy. While there are no instruments in hemophilia which addresses this latent construct, there are many examples of how instruments for these groups can be developed to meet Rasch standards. A recent example in the Alzheimer Patient Partner Life Impact (APPLIQue) questionnaire, a needs fulfillment instrument for caregiver quality of life which has the required Rasch interval measurement properties and can be translated to a bounded ratio scale.

The point to note is the commitment to assumption driven cost-per-QALY simulations where the exercise assumes these instrument scores have implicit (i.e., assumed) bounded ratio properties. ICER is not alone in presenting assumption driven cost-effectiveness claims for hemophilia therapies, including gene therapy; studies keep on surfacing, producing different claims for the same therapy areas and, presumably, will continue to do so, even as marketing exercises. They all rely on Markov modeling or similar assumption driven simulations to create imaginary claims. A common feature, as with ICER, is to base the claims on incremental cost-utility models; there is no perception of the limitations of fundamental measurement in the application of ordinal preference score and the impossibility of the QALY as a construct. The fact that the value claim for cost-effectiveness is not empirically meaningful does not appear to be an issue. Systematic reviews of these various modeled hemophilia studies also fail to recognize the limitations imposed by fundamental measurement and the importance of value claims that are credible, evaluable and replicable. A systematic review by Drummond et al is of interest as it illustrates to this lack of awareness or even interest in the required standards. Pointing to what is seen as deficiencies in assumption driven simulations in hemophilia, to include overlooking heterogeneity in the patient population, the absence of treatment strategies and inadequate control for confounders, the authors propose a set of 12 standards, based on the CHEERS format, to make the modeled simulations with their imaginary cost effectiveness claims more helpful to decision makers. These include basing the evaluation on systematic reviews, assessment over the lifetime of a target group, using a generalized measure of benefit (i.e., QALYs) and characterize uncertainty through probabilistic sensitivity analysis. Whether these CHEERS plus standards can be considered a basis for an imaginary assumption driven simulation being ‘more helpful’ is a moot point as there is no interest expressed in the standards of normal science and the limitations of...
fundamental measurement with the application of RMT. A subsequent systematic review merely reinforces this commitment to non-science in value claims although admitting that methodological variations among the more recent studies and difference in treatment schemes made comparative assessments difficult. At least, with this diversity, decision makers will not be spared loss of choice in these ‘helpful’ imaginary cost-effectiveness claims, although there is the perennial concern with bias and the reverse engineering of imaginary claims in hemophilia.

The hallmark of the ICER approach to evaluating and unequivocally claiming cost effectiveness at pricing points is that it is built entirely on arbitrary assumptions. The problem with assumptions is that there can be no claim that one bundle of assumptions regarding future modeling for cost-effectiveness can be claimed to be superior (or ‘more realistic’) than another. This is a trivial point, but one that is typically ignored. Recent systematic reviews of cost-utility assessment of hemophilia therapies have found, as expected, considerable variation in modeled claims. Thorat et al, for example, in a further systematic review of models to support claims for the overall value of hemophilia treatment based on cost-utility analyses found that cost-effectiveness claims for treatments varied widely based on variations in study design, including differences in time horizon, discount rates and medical interventions; a conclusion that echoes an earlier systematic review by Valente et al concluding that: These studies reported remarkably different results, using utility values based on different assumptions and data sources.

These results are entirely expected; they follow from the commitment in HTA to the construction of modeled approximate information to support formulary decisions. Hypothesis testing was put to one side in favor of assumption-based evidence to support cost-effectiveness claims and formulary decisions; this means there is no coherent basis for empirically assessing competing claims as would be with hypothesis testing with empirical claims. A denial, therefore, of the standards of normal science and progress driven by the process of conjecture and rejection. We can forget attempts to impose standards for modeling; the claim that we have reference case standards is too open ended to be of any use given, for example, the opportunity to apply a range of utility scores and even reverse engineer the modeled claims. The result is what may be described as an ‘open season’ for imaginary cost-utility models in hemophilia; none of which should be taken serious by formulary committees. This means rejecting the notion of imaginary blanket cost-effectiveness claims and adopting a single attribute, protocol driven value assessment framework for specific product claims in hemophilia, whether these are in clinical, quality of life or drug and resource utilization terms.

**RASCH, PROMIS AND ITEM RESPONSE THEORY**

Item response theory (IRT) and the Patient Reported Outcomes Measurement Response System (PROMIS) item bank and proposed item sets are of limited use in target patient population outcomes assessment. In the case of IRT and PROMIS, various items and instruments are not designed to produce interval scores with the possibility of a translation to a ratio score. Certainly, there is a potential application of the PROMIS item bank as a key part of the recommended instruments for the health outcomes set in hemophilia, linked to hemophilia specific items (van Balen et al, Table 35) and the application in hemophilia target groups of T-statistic distributions, including capturing individual claims for response to therapy; but this is as far as we can go for
both dichotomous and polytomous PROMIS item or IRT constructs until RMT required standards are applied.

The reason for this limited application, judged from a Rasch perspective, where the Rasch model should not be considered as the one-parameter logistic model (1PL IRT), as the approach to conceptualizing the relationship between data and theory. IRT, in common with Classical Test Theory (CTT), is focused on fitting a prior model to the available data to create items; the objective being to report the best fit even if this involves the introduction of supplementary model parameters. Rasch is conceptually and paradigmatically distinct with the primary focus on meeting standards for fundamental measurement where data items have to meet the Rasch model specification to support reasonable interval-measured conclusions and inferences from the data. Data collection, the choice of items, must be guided by Rasch considerations. This points to the distinction between fitting a model to the data and, in the Rasch approach, selecting data items to fit the model. This distinction is important because it points to a fundamental difference between IRT and Rasch measurement. Thus, while PROMIS/IRT models are ‘exploratory and descriptive’; Rasch models are ‘confirmatory and predictive’ where the data are required to confirm the model. The focus in Rasch modeling is on the size and structure of residuals to confirm that the principles of conjoint simultaneous measurement have been realized sufficiently to justify the claim that the measure of a latent construct has invariant interval properties. This applies to both dichotomous and polytomous instruments where the requirement is to calibrate instruments. We are not concerned as with IRT to fit the model to data to minimize residual variance. This does not mean we drop items in the Rasch model fitting willy-nilly, but attempt to find out, in terms of the latent construct, why an item is apparently redundant. The bottom line, as Andrich would argue, is that the Rasch and PROMIS/IRT approaches are incompatible paradigms 21, 22. The Rasch measurement model is the only accepted framework if our object is fundamental measurement; IRT and PROMIS are redundant.

If the Rasch model is taken as the exemplar framework for both dichotomous and polytomous PROs, the question that can then be addressed is the extent to which PROMIS or IRT based instruments fall short when evaluated in terms of the criteria that RMT requires to judge whether or not the PROMIS item-selected instrument meets Rasch requirements; in particular in respect of item-based polytomous instruments. While there is no hard and fast template for conducting a Rasch analysis of existing polytomous instruments the following elements should be part (and are supported by assessment software such as RUMM, WINSTEPS and R) of an assessment to evaluate whether or not the instrument has properties that may be considered an acceptable approximation to an interval score 23.

• Overall instrument and item functioning
• Unidimensionality of underlying construct
• Local independence of items
• Category and threshold functioning
• Differential item functioning
• Person and item alignment

While the extant literature is limited, in part because professional groups such as ISPOR have not addressed the issue, two recent studies are, hopefully trail setters in this ex post facto assessment
of PROMIS type instruments in the cases of depression and fatigue\textsuperscript{24,25}. These assessment
directions, respectively, the IRT 28 and 51 item depression scales and the IRT fatigue scale.; both of
these are part of the core PRO set proposed for hemophilia. The results of these two analyses are
not encouraging. While there is no magic threshold given the criteria and the degree of overall
subjectivity involved, the results for depression point to a number of significant deficiencies
involving item fit, failure to capture the latent trait of interest in sample of responses to scale
targeting (e.g., for those with lower depression) which were not resolved with the 51-item scale
compared to the 28-item scale and the absence of a single construct. While the depression scales might be
improved by item re-assessment, the scales were unsatisfactory, even to considering additional
conceptual categories of depression. The fatigue scale assessments were broader involving the
FACIT-F scale, the SF-36 vitality scale and the LupusQoL Fatigue instrument. The results
challenged the use of all three instruments; they were not considered suitable for clinical
assessments. Item fit was poor, even when a selection of the best-performing items was made. The
FACIT-F total score was considered inadequate with multiple underpinning concepts. The SF-36
vitality and LupusQoL Fatigue scales failed to address relevant fatigue issues leading to a lack of
precision in the scores.

On the positive side there is now a growing literature, notably in the area of rehabilitation medicine,
that has addressed the issue of establishing Rasch standards for instruments and the evaluation of
existing instruments in target patient populations or disease areas. Most recently the publication of
the Rasch Reporting Guideline for Rehabilitation Research (RULER) that is intended to ensure
authors, reviewer and editors have uniform guidance about how to write and evaluate research on
rehabilitation outcomes assessments in terms of six psychometric Rasch domains\textsuperscript{26,27}. These
include conceptual content (e.g., unidimensionality; structural validity (e.g., latent trait); rating
scale step structure; overall model and individual item fit; and measurement invariance,
reproducibility and reliability for differential item functioning.

**RASCH AND HEMOPHILIA OUTCOMES**

Once we accept the need to meet the standards of normal science, including fundamental
measurement, we have to accept the imperative of a RMT ‘filter’ to accept value claims. Clearly,
there will be clinical value claims (e.g., bleed rates) which will meet ratio properties, as well as
claims for drug and resource utilization. It is the latent construct patient outcome claims that
present a challenge. These must meet Rasch measurement standards. This requirement is,
unfortunately absent from the criteria applied in outcome measures by ICHOR and others, despite
their apparent commitment to a program of long-term research in hemophilia. Meeting the
standards of fundamental measurement is a necessary precondition to therapy evaluations, it must
rest, in patient reported outcome claims, on a sound theoretical foundation; one that is missing in
non-evaluable ordinal cost-utility claims instruments. There is an important distinction between
the pragmatic \textit{ex post facto} application of the Rasch model and a commitment to Rasch in the
process of instrument development. This supports the role that Rasch measurement can and must
play in instrument development.

Patient centric value claims in hemophilia face a critical hurdle: do they meet the required
measurement properties, either ratio or interval. The key question: what are we trying to measure
in hemophilia? If we are to develop items and their selection then we must understand the nature
of the possible latent traits and whether they can be measured following RMT. Those proposing core measures in hemophilia have a long way to go. There are a number of examples of measures which have unknown measurement properties and for which, as a default position, we must accept as only ordinal scores which have no role in evaluating response to therapy.

Likert-based polytomous instruments in hemophilia for which we must assume only ordinal properties include: (i) the Haem-A-QoL (adult) and Haemo-QoL (pediatric) instruments which rely on the summation of integer scores from Likert response scales (some reordered) with subscales and an overall score to create composite total raw and transformed ordinal scores; (ii) the Canadian Hemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT) version 2.0 (youth), with a recent revision to version 3.0 (youth) with 40 items and seven domains with Likert integer summed sub-scales and total score standardized to 100; and (iii) the Hemophilia Activities List (HAL) designed to measure the impact of hemophilia on self-perceived functional abilities in adults with hemophilia has 42 Likert items in seven domains where the most important outcomes are overall integer sum score and three component scores for upper extremity activities, basic lower extremity activities and complex lower extremity activities, with each domain also scored and, more recently, a shortened version of 18 items.

Despite considerable attention given to what various authors judged the appropriate psychometric tests for these instruments over some 20 years the question of fundamental measurement was never addressed. Indeed, claims have been made that the composite ordinal scores (i) and (ii) above, are [multiattribute] health related quality of life measures (HRQoL). This is mistaken as they fail the Rasch standards for a unidimensional latent construct with interval properties, let alone the application of a polytomous Rasch assessment.

**PROTOCOLS**

Value claims for hemophilia therapies should be accompanied by a protocol detailing how the claim is to be assessed; this applies equally to patient-centric outcomes as it would to purely clinical, drug and resource utilization claims. This notion appears to be absent from the value-based health care methodology endorse by ICHOM and by advocates of PROMIS; it clearly does not apply to modeled simulations or other techniques that yield only imaginary value claims. This is the importance of meeting the standards for fundamental measurement, the application of Rasch modeling in hemophilia outcomes, to establish a real-world evidence basis for therapy choice and the basis for ongoing research programs and even outcomes-based contracting. Judged from this perspective we have to conclude that assumption driven simulations, although claimed to be ‘helpful’ to an unknown and unknowable degree, in health care decisions are a barren undertaking. There is no basis for progress in our understanding of the benefits of competing therapies or, what Popper would describe, as the evolution in objective knowledge. This applies not only to patient reported outcomes to include quality of life of patients and caregivers, but to purely clinical claims defined in ratio terms and those for drug and resource utilization.
CONCLUSIONS

If we are to accept the relevance of patient centric instruments in hemophilia then we have to recognize the importance of Rasch measurement. As stated by Wright, and quoted by Bond, Rasch models are the only laws of quantification, that define objective measurement, determine what is measurable, decide which data are useful, and expose which data are not. There are minimum standards for measurement which must apply for both dichotomous and polytomous hemophilia instruments irrespective of the target patient population. While ICER is committed to assumption driven simulations and generic ordinal preference with impossible cost-per-QALY calculations and thresholds, these criticisms apply equally in hemophilia with what appears to be a complete neglect of fundamental measurement. RMT is central to this endeavor. There needs to be a complete rethink of the standards required for hemophilia instruments (c.f., rehabilitation research) to assess therapy response for both pediatric and adult populations; to include caregivers. The proposed core measures will fail unless it can be demonstrated that they meet, or are a reasonable approximate to Rasch interval standards. If the existing instruments cannot be defended then new instruments must be devised to meet Rasch standards (e.g., needs fulfillment quality of life).

It clear that if we are to meet fundamental measurement standards then we must subscribe to the RMT not the IRT approach to instrument development. It would appear, therefore, to be incumbent upon ICHOR to insist is its recommendations for core instruments to factor in the Rasch criteria for both instrument appraisal and recommendations for development, support by assessment protocols. While this is, probably, at least 40 years overdue, the credibility of recommendations rests on this commitment. Until we achieve these standards the absence of acceptable measurement will prejudice therapy response claims and proposals for ongoing research strategies for new therapies, including pathbreaking gene therapies in hemophilia.

REFERENCES


12 Langley P, McKenna S. Fundamental measurement: The Need Fulfillment Quality of Life (N-QOL) Measure. *InovPharm*. 2021;11(3): no. 17


18 Langley P. Facilitating bias in cost-effectiveness analysis: CHEERS 2022 and the creation of assumption-driven imaginary value claims in health technology assessment [version 1; peer review: 2 approved]. *F1000Research* 2022, 11:993


