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REJECTING PSEUDOSCIENCE: TEN COMANDMENTS FOR RARE DISEASE PRICING AND REIMBURSEMENT

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ABSTRACT

If a formulary submission is to meet the standards of normal science and fundamental measurement then there are ten key points … or commandments … that must be recognized. This sets the stage for the rejection of the standards that have been in place for the past 30 years in health technology assessment (HTA) which have endorsed the creation of approximate information created by assumption driven model simulations. It has always been a puzzle as to why decision makers should be prepared to accept claims that are entirely imaginary and have no prospect of ever being empirically evaluated. Certainly, the leaders in the field of HTA, notable academic leaders, have never questioned the role of imaginary claims; possibly because they believe, mistakenly, in the realism of assumptions to drive models projecting decades into an unknown future. Unfortunately, this odd belief is widespread, not only among the academic community, but in government agencies and with manufacturers. The purpose of these ten commandments is to try and bring some sanity to what is an absurd belief system and one, it should be emphasized, that has particularly deleterious consequences for manufacturers of rare disease therapies, who face limited data at product launch. They are, if you like, sitting targets for assumption driven models with recommended price discounts and access controls all resting on the mathematically impossible quality adjusted life year (QALY). We have to do better; this is the focus of the NEW START formulary submission recommendations, summarized by these ten commandments.

INTRODUCTION

Health technology assessment (HTA) has relied on imaginary pseudoscientific claims for over 30 years; supported by leading academic institutions [1]. HTA practitioners have accepted a belief system that rests on assumption driven modeled simulations to create imaging cost-per-quality adjusted life year (QALY) and thresholds to support recommended imaginary process and access controls for rare diseases and a range of other therapies for chronic conditions. Epitomized by the claims presented by the Institute for Clinical and Economic Review (ICER) formulary committees, PBMs and MCOs have been asked to rely on invented and non-evaluable claims to the exclusion of the standards for normal science and a commitment to progress in therapy claims. This is unacceptable. We need a NEW START in formulary submissions in rare disease and other chronic conditions that support value claims that are robust and meaningful [2]. Overturning 30 years of wasted efforts is not easy; the belief system is firmly entrenched. Following Moses and the Mt Sinai revelation, the fatted golden QALY calf must be overthrown. Focusing on 10 commandments for value claim standards is a necessary first step to support rare disease pricing and reimbursement: the key is measurement

COMMANDMENT I: VALUE CLAIMS

All value claims for rare disease products must conform to the standards of normal science and fundamental measurement as detailed in the NEW START formulary submission guide

The recognized standards for normal science, that all claims must be credible, evaluable and replicable, have been in place since the mid-17th century: the Royal Society of London (founded 1660) has as its motto *nullius in verba* or take nobody's word for it. This is accepted in the physical science and advanced social sciences such as economics and is the foundation for the discovery of new, yet provisional facts. This has to be our focus.

Unfortunately, the imaginary claim belief system is well entrenched. There is an all too familiar mind set that rejects out of hand any attempt to challenge the belief in the pre-eminent role of invented model claims at product launch and throughout the product life cycle. If new data are presented these have no more impact than to modify assumptions in the model. This illustrates the fundamental flaw: there is no unique model driven by some odd belief in the realism of assumptions to support claims for an unknown future; as a point in logic, the fact that all past futures have resembled past pasts does not mean that all future futures will resemble future pasts. Potentially, there are a multitude of possible ICER models each coming to different conclusions.

COMMANDMENT II: SINGLE ATTRIBUTES

All value claims must be for single attributes whether they are clinical, patient reported outcomes (PROs) or for drug and resource utilization

An appreciation of the standards of fundamental measurement sets the stage for the two premises that support the NEW START formulary submission guidelines [3]. These are:

- **All value claims for a product or therapeutic intervention must refer to a single attribute that meets the demarcation standards for normal science: all value claims must be credible, evaluable and replicable**
- **All value claims must be consistent with the limitations imposed by the axioms of fundamental measurement: they must be unidimensional and meet interval or ratio measurement standards**

These premises apply to value claims that are disease or target patient population specific, where every claim is supported by a reporting and assessment protocol. Multiattribute claims

unless the components are all single attribute calins that meet the standards for fundamental measurement, are unacceptable.

COMMANDMENT III: MEASUREMENT

Unless value claims are expressed as single attributes with ratio or interval measurement properties they should be rejected

Consider the following statements by Lord Kelvin (William Thomson 1824 – 1907)

> **"To measure is to know."**
> **"If you cannot measure it, you cannot improve it."**
> **"When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind."**

Measurement is key. We must reject nominal and ordinal measures and accept only interval or ratio. These last two can support response claims; ordinal measures, which are widespread in HTA, cannot support response to therapy claims. Nor can they support arithmetic operations; the QALY that requires preference or utility measures to be ratio scales fails as they are ordinal. The QALY should be rejected; it is mathematically impossible[4] .

COMMANDMENT IV: FILTER

All value claims must be filtered and assessed to reject nominal or ordinal scales.

Again, take nobody's word for it: in this case the measurement standards for outcome claims: clinical end points are either in ratio or interval form; PRO claims must be in interval or ratio form while drug and resource utilization claims must be in ratio form. A ratio scale has interval (invariant) properties and a true zero (Kelvin temperature with approximate absolute zero); fahrenheit and centigrade are interval measures).

PRO claims typically fail these standards: all multiattribute preference scales and most disease specific scales are ordinal scales; this is unacceptable. An ordinal scale can rank scores but we do not know difference between scores; it cannot capture response to therapy (e.g., EQ-5D-3L/5L) or the creation of QALYs.

The problem is that instrument developers have seemed singularly unaware of the standards for fundamental measurement. They fail to appreciate that if an instrument is to have interval or ratio measurement properties then it has to be designed to achieve that standard. With

PROs this means meeting the standards for modern or Rasch measurement theory and the application of conjoint simultaneous measurement [5]. This is what a filter has to confirm; otherwise, it is rejected. PRO claims typically fail these standards: all multiattribute preference scales and most disease specific scales fail as they are all ordinal scales. An ordinal scale can rank scores but we do not know difference between scores; it cannot capture response to therapy (e.g., EQ-5D-3L/5L) or the creation of QALYs, with QALY based non-evaluable value claims.

COMMANDMENT V: VALUE CLAIMS PROTOCOLS

Each value claim should be accompanied by a protocol detailing how that value claim is to be empirically assessed and reported in a meaningful time frame

The belief system of imaginary HTA claims fails because it is impossible to propose a protocol to set out how that imaginary claim is to be empirically assessed; as these typically extend decades into the future the exercise is futile.

Unless a value claim is accompanied by an assessment protocol acceptable to health system decision makers it must be rejected. The value claim establishes credibility, with the ability to be empirically evaluated and replicated. A protocol, the essence of RCT claims for new products, sets the stage for progress in the disease area for the discovery of new, yet provisional facts, for the therapy intervention. The same standard must apply to all NEW START value claims.

Consistent with the standards of normal science, the product must be open to disease area and therapeutic class reviews over its patent life or life cycle; a protocol sets the standards for these reviews.

COMMANDMENT VI: PATIENT REPORTED OUTCOME CLAIMS

All Patient Reported Outcome value claims must be disease or target patient population specific and capture the patient or caregiver voice

Only a handful of PRO measures reach this standard. To evaluate response to therapy for patients in a disease state or a target patient population, patient or caregiver needs and their fulfillment, subjectively articulated by patients are the critical input.

Clinician proposed clinical end points must be addressed separately as single attributes. The needs fulfillment latent construct, specific to the target patient population, is the only one that meets the required measurement standards

Needs fulfillment is a holistic quality of life attribute that rejects multiattribute health related quality of life (HRQoL) measures (e.g., EQ-5D-5L) in favor of a subjective evaluation of the needs of patients/caregivers in a disease area and the extent to which these are met. It applies the conjoint simultaneous measurement of Rasch theory which combines the difficulty of a need being met and the ability of patients/caregivers to meet that need given a therapy intervention

COMMANDMENT VII: PREPARATION

At initiation of Phase 3, with protocols for pivotal claims, companies must have determined the value claims proposed for their product

Manufacturers in rare disease must decide, possibly following discussion with health systems, on the required value claims to support (i) clinical, (ii) PRO; (iii) drug utilization and (iv) resource utilization impacts and their respective protocols. This should be an integral part of product development, notably as an input to pivotal claims protocol designs.

Investments need to be considered for PRO instruments to meet measurement standards. Early agreement should focus on a formulary submission package to justify choice of evaluable value claims, including comparative claims

COMMANDMENT VIII: PRO INVESTMENT

Manufacturers should be prepared to commit to investing in PRO value claim instruments that meet required measurement standards, capturing the patient and caregiver voice

Needs fulfillment instrument capturing both interval and bounded ratio value claims are the only acceptable PROs with needs expressed in terms of the items (dichotomous) identified following subject assessment and application of Rasch techniques to identify instrument item fit

Value claims expressed as the distribution of respondent's needs being met (in a current bounded ratio analysis of caregiver needs fulfillment for spouses with Alzheimer's disease) average needs-fulfillment achieved was only 0.3 (scale 0 – 1) with 25 item needs tabulated

capturing Needs-Quality of Life (N-QOL). This will support detailed assessment of caregiver and spousal characteristics impact on need fulfillment,

COMMANDMENT IX: ABANDONING MODELS

Unless a model can create evaluable claims that can be captured by a protocol for assessment and reporting, the model must be rejected

Non-evaluable assumption driven simulated claims (e.g., ICER) must be rejected out of hand; they fail both the standards of normal science and fundamental measurement. ICER models and those employed elsewhere in HTA are an analytical dead end

Manufacturers should not engage with ICER or any other modeling group unless the required standards for normal science and fundamental measurement are met

Manufacturers, notably with rare disease, must defend their choice of the NEW START formulary submission package, detailing why the ICER approach is irrelevant to the development of a research program and the Discovery of new, yet provisional facts regarding their product and its value claims

Manufacturers must ensure they are equipped to drop notions of overall product cost-effectiveness (at thresholds for cost-per-QALY pricing) in favor of single attribute protocols supporting their value claims

COMMANDMENT X: NEGOTIATION

All value claims must be presented with contractually agreed timelines to support evaluation and replication as well as meeting measurement standards

The value claim package is a critical step in both replicating RCT based claims as well as meeting, provisionally, key evidence gaps at product launch for all value claim: clinical, PRO and drug and resource utilization

Third party assumption driven modeled pricing and access recommendations (e.g., ICER) must be rejected with the case for rejection presented in negotiations

All pricing is provisional; prices must be agreed subject to value claims feedback in a meaningful time frame

Negotiations will be ongoing, subject to requests for additional data as part of disease area and therapeutic class reviews

CONCLUSIONS: TRAINING

If these ten commandments are to be met successfully and the NEW START package implemented manufacturers should ensure that the staff involved are familiar with the techniques and insights that support NEW START. Consideration should be given to training. This applies to the product development phase, notably in the choice or development of PRO instruments to support quality of life.

Consideration should be given to the in0line NEW START training package[6]

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