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FORMULARY SUBMISSIONS: VALUE CLAIMS, PROTOCOLS AND OUTCOMES BASED CONTRACTING IN RARE DISEASE

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Abstract

Outcomes based payments contracting is in its infancy. The increased attention being given to rare disease places a premium on the ability to engage with payers to ensure that there is an analytical framework relevant to value claims contracting. Rare disease is not, of course, alone; many other chronic disease sates may be suitable candidates and have been over the past 10 years or more. Rare disease, however stands apart: (i) the evidence base at product launch is limited; (ii) the therapy costs are often considered prohibitive; and (iii) the target patient population is small. At the same time, those seeking to implement an evidence-based engagement with health systems to support innovative rare disease interventions face a substantive barrier. The obsession or meme in health technology assessment (a.k.a pharmacoeconomics) with assumption driven modeled cost-effectiveness simulations that support imaginary recommendations for cost-effective pricing and access. In the US this barrier is the business model of the Institute for Clinical and Economic Review (ICER) and one endorsed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Rate disease can be better served with tools at our disposal with a new start in health technology assessment. The purpose of this brief note is to make the case that a proposed new start in health technology assessment focused on single attribute value claims that meet the standards of normal science and fundamental evidence can not only dispense with the ICER imaginary modeling but with a new start formulary submission package, integrate value claims with assessment protocols to set the stage for effective outcome-based contracting as the default standard for future payer negotiations.

INTRODUCTION

Value claims for pharmaceutical products and devices to support outcomes contracting, in particular in rare disease can only be understood if we are clear about the standards that must be applied in the development, application and evaluation of instruments to capture response to therapy within the many rare disease and therapy areas [1]. If a value claim, whether it is for clinical outcomes, patient reported outcomes (to include quality of life), drug utilization or resource utilization, is to support formulary submissions and, in the longer run, outcomes contracting to support pricing and access recommendations, then it must meet the standards for normal science, including fundamental measurement. These requirements are critical in rare disease where the focus on closely targeted therapies not high prevalence chronic conditions where we have, in the

past focused on 'blockbuster' therapies; where outcomes contracting has been essentially ignored. The unique status of targeted rare disease product represents a game change. Close attention needs to be given to the structure and content of formulary submissions, the standards of value claims and, in the longer term, protocols to accompany those claims; protocols that detail the process of claims tracking and reporting for health systems and contracting partners who understandably seek to attempt to minimize risk and defaults in outcomes contracting for rare disease.

The purpose of this brief commentary is to detail the required standards for value claims in rare disease, the importance of a formulary submission that promotes evaluable value claims and the place of protocols to support those claims and prospective outcomes contracting. To date, there has been limited efforts to introduce outcomes contracting in rare disease. Perhaps this not for want of trying, but the reason may be more basic: the absence of an agreed set of rules to support formulary submissions where a balance has to be sought, favorable to all parties, between the obvious need to recoup development costs by the manufacturer and the equally obvious concern of the health system that the needs of patients and caregivers are met. Needs, it might be added, that are broader than the those articulated by clinician. The commentary is in three parts: (i) a statement of the required analytical standards for value claims; (ii) the barrier raised by the current belief system in health technology assessment for claims to be based on imaginary assumption driven simulation models; and (iii) the required structure and content of formulary submissions to support value claims in rare disease and potential outcomes contracting.

STANDARDS FOR VALUE CLAMS

If we accept the standards of normal science for credible, evaluable and replicable value claims, together with recognition of the limitations of fundamental measurement, then we must recognize two essential premises for any disease specific value claim:

- All value claims for a product or therapeutic intervention must each 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. It should be emphasized that value claims are not one-off statements of anticipated impact; rather they must be seen as provisional, subject to review and the outcomes of tracking and contracting, to set the stage for further discovery of 'new facts' as they apply to that rare disease. Ideally, the engagement between a manufacturer in a rare disease must be for the life of the product or as long as the health system sees a benefit from its place on formulary.

Measurement is critical. As detailed in previous commentaries in *Innovations in Pharmacy* value claims for specific attributes may have interval or ratio measurement properties; if not then we have no basis, as with ordinal measures, for evaluating response to therapy [2] [3]. As outcomes contracting is focused on response, and agreement on the validity of the proposed response

measure, then we need agreement on the appropriate standards. The corollary here is that if we insist on these standards for measurable single attributes then we must reject multiattribute preference scores such as those for the EQ-5D-5L (and the preference base QALY) as well, as the majority of disease specific instruments that have only ordinal scores [4]. This points to a fundamental issue in rare disease: if the needs of patients and caregivers are to be evaluated and response captured, then new instruments are required. There are a number of examples of instruments that meet the required measurement standards; in the case of patients' needs, an example is the, Psoriatic Arthritis Quality of Life Questionnaire (PSORIQoL) [5] and, for caregivers' needs, the Alzheimer's Patient Partners Life Impact Questionnaire (APPLIQue) [6 7] .

THE DEMISE OF BELIEF IN HEALTH TECHNOLOGY ASSESSMENT

One of the most puzzling decisions in health technology assessment (or pharmacoeconomics) was to reject hypothesis testing in therapy evaluations in favor of creating approximate information to support formulary decisions; a position endorsed by the leading professional organization, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [8] . In the US, this decision is seen most clearly in the activities of the Institute for Clinical and Economic Review (ICER). There are regular evidence reports from ICER proposing pricing and access recommendations based on assumption-driven QALY focused modeled simulations that lack any credibility when judged against the standards of normal science and fundamental measurement [9]. This is of particular relevance in rare disease where the models have been applied to rare disease therapies; all too often proposing significant price reductions and even limitations on product access in order to conform to cost-per-QALY thresholds applied to incremental cost-per-QALY claims. The entire ICER modeling exercise, typically undertaken by consultant academic groups, is a charade. It produces imaginary claims based on the QALY, a mathematically impossible construct as well as time horizons which by design were never meant to produce empirically evaluable claims; there is no concept by ICER of the role of value claims to support outcomes contracting. The ICER imaginary models have, to say the least, no place whatsoever to support outcomes contracting for value claims. Contacts are not entered into when the so-called value claim is a will o'the wisp phantasm [10]. Unfortunately, too many (notably in the media) take the ICER pronouncements at face value; a loss for both manufacturers in rare disease as well as patients and caregiver.

Yet ICER continues although advised on numerous occasions that they are promoting nonsense; they have nowhere else to go and, in concert with thousands of believers in approximate information modelling, no one is prepared to admit that for 30 years health technology assessment has been a waste of time. A new paradigm for technology assessment is overdue; one that has the potential to support robust value claims and outcomes contracting in rare disease.

A NEW HEALTH TECHNOLOGY ASSESSMENT FRAMEWORK

If outcome-based value claim contracting is the new standard, in particular for rare disease, then we have the required analytical tools to ensure its potential success. Rare disease presents issues that are not found in more prevalent disease states: the question of defining a target disease population, issues of heterogeneity in population characteristics and prospective defining therapy response, the absence of data at product launch, limited comparator options and ill-defined

standards of care, anticipated compliance with therapy, the time frame for tracking therapy response and limited tools to capture quality of life defined in terms of patient and caregiver needs. These are not unattainable objectives but require a commitment to the standards proposed for value claims and a willingness to invest in tracking those claims; if necessary, as part of an outcomes contract.

If value claims are to support effective contracting, then the choice of value claim must begin as early as Phase 2 in product development; protocols for phase 3 pivotal trials must reflect the choice of value claim and its congruence with the needs of patients and caregivers, together with those of the health system. The first step must be to decide on the categorization of value claims: clinical, PRO, drug and resource utilization. While it is easy to maintain that clinical claims, measured in interval or ratio terms, are a first call, it is important to agree these and ensure that they have the required measurement properties. There is, of course, a grey area between exclusively non-PRO clinical endpoints and PRO endpoints used by physicians to judge therapy response, yet all proposed measures must meet the required standards. This is critical because the overwhelming majority of PRO instruments used to assess therapy response fail to meet the required measurement standards [11] [12] [13] [14]. Indeed, if there is a proposed core of instruments proposed for assessing response in a rare disease these must all be subject to the same scrutiny.

Value claims for quality of life, either for the patient or, more usually in pediatric rare disease therapy targets, the caregiver present a number of issues, First, it is absurd to consider any of the generic multiattribute instruments; none have the required measurement properties as they product composite ordinal preference scores. This means value claims in terms of QALYs are also to be rejected; together with any thought of attempting to emulate the ICER approximate information models with imaginary lifetime claims [15]. Instead, consideration should be given to the concept of needs fulfilment: to what extent are the subjectively assessed needs of patients and/or caregivers met in the absence of a new therapy and to what extent are these needs resolved through application of the therapy. Taking this path introduces the application of Rasch measurement or modern measurement theory [16]. Widely applied for the past 60 years in education and psychology, and to a limited extent for PRO instruments in health technology assessment (with many misapplications), the appropriate application involves creating an instrument that considers the likelihood of a positive response in terms of the difficulty of a need and the ability of the patient or caregiver to resolve that need with a new intervention. The Rasch models yields interval scores; it is now possible with a recently developed algorithm to translate these to a bounded ratio score [17]. For the first time we have a true quality of life score that can yield, if required, the equivalent to a QALY measure. There are now some 25 plus disease specific need fulfillment instruments available; few in rare diseases. This demonstrates the ability to create a disease specific instrument; but one that needs to be considered at phase 2 to allow time for development. If the measure is successful for the selected need fulfilment attribute in a rare disease, then this could be a key factor in product acceptance subject to instrument application and replication.

Value claims for drug and other resource utilization are more straightforward. Claims should be for specific attributes, I.e., for units defined by drug and procedure codes. Given access to the appropriate data bases, with target populations defined in terms of ICD-!0-CM or ICD-11 codes, it should not be difficult to propose value claims for product uptake, switching from comparator products and estimates of compliance with therapy. These would all be ratio measures.

QUESTIONS TO BE ASKED

Preparing and presenting value claims to lay the groundwork for possible outcome-based contracting is not one sided. It is important that formulary committees or their equivalents should be prepared with a list of questions to be submitted to the manufacturer to ensure that the required standards for credible, evaluable and replicable claims that met interval or ratio standards should be met. In the case of PROs, notably needs fulfillment claims, the health system needs to be assured that the instruments (items and binary response options) are consistent with the Rasch models application of conjoint simultaneous measurement. This is not only an insurance protection for the formulary committee but it will hopefully ensure that the manufacturers' meet the required standards. After all, given the potential cost to the manufacturer of implementing and reporting outcomes, a lack of appreciation of the importance of utilizing appropriate measurement standards could be evidence of prospective contractual failure.

CONCLUSIONS

It must be emphasized that the concern is not with the ability to claim a new therapy is cost-effective; this is an outcome claim that is not only mathematically impossible but one that fails to yield valid value claims. Rather, in rare disease, we look to a selective choice of value claims, a portfolio, each of which can be the subject of a protocol base evaluation to support contracted pricing and access. A key element in the creation of value claims is to focus on evidence gaps; covering clinical, quality of life and resource utilization; if data are not available at product launch to enable rapid assessment and reporting of value claims, then outcomes contracting must look to data assembly to support claims over the longer term. Falling back on ICER modelled imaginary approximate information claims is no substitute; after all, there are any number of competing modelled claims that could be created, none of which could have a preferred non-evaluable claim for future realism over any other as they are all assumption driven. From the manufacturer's perspective ICER and its claim for invented evidence is a major barrier; this must be faced down in the interests not only of the manufacturer but the patient and caregiver in rare disease. We have the required framework for rare disease submissions and the contractual framework to support and evaluate contracted value claims.

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