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EVIDENCE FRAMEWORK FOR RARE AND CHRONIC DISEASES

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Abstract

The past 30 years have witnessed an insistence on the part of groups such as ISPOR in health technology assessment that the way forward is to reject hypothesis testing in favor of the construction of imaginary worlds to provide 'approximate information' to formulary decision makers. This is a ridiculous position. It rejects the role of discovery that has been the core of normal science in the four hundred years since the scientific revolution, the invention of science, in the seventeenth century. We are now at a major decision point: do we reject normal science or do we reject the pseudoscience of health technology assessment, led in the US by the activities of ICER. The argument presented here is that we must reject intelligent design in favor of natural selection.

Introduction

Considerable effort has been expended over the last few years to engage with the Institute for Clinical and Economic Review to take more than a cursory interest in rare and chronic diseases. This is seen in the attempts by patient advocacy groups to convince ICER to take explicit account of the impact of new and innovative therapies in the ICER value assessment framework. That ICER should take this approach will come as no surprise. The ICER business model, in fact ICER's existence, depends on their incremental cost-per-incremental-quality adjusted life year (QALY) lifetime modeling construct. As an eager acolyte of the Institute for Pharmacoeconomics and Outcomes Research (ISPOR), ICER has embraced their commitment to constructing imaginary worlds. As detailed in previous commentaries, the ICER approach does not meet the standards of normal science [1]. Attempts to convince ICER to amend its model are a waste of time. We need an entirely new approach to assess response to therapy in rare disease, particularly if the quality of life of patients and caregivers are a critical variable.

The ICER Value Assessment Framework

The reason the ICER value assessment framework fails is because it fails to meet scientific standards criteria for credibility, evaluation and replication. The claims made by ICER fail the demarcation test between science and pseudoscience. They share the Dover courtroom with intelligent design. The foundations of science rest on hypothesis testing and the discovery of new, yet evaluable facts. ICER rejects this. The imaginary lifetime model is intended to overwhelm formulary committees with 'approximate information' – or disinformation. There is no way to distinguish one from the other. When there is nothing to approximate to, unless it is the X-files 'the truth is out there', the phrase is meaningless.

But there is a fatal flaw in this value assessment package. There is no such entity as a QALY. Consider: the QALY is created by time spent in a disease stage multiplied by a 'utility' score in the range 0 – 1. According to the axioms of fundamental measurement, this is high school mathematics, if you want to multiply a quantity (months in a disease state) by a utility score, the score has to have ratio properties (a true zero). No value can be below zero. While this may be difficult to grasp, the fact is that the utility score used by ICER (the EQ-5D-3L) allows for negative utilities. The utility values for the EQ-5D-3L measure fall in the range 1 to -0.59. The QALY cannot be created. The axioms are denied. The utility score is actually a manifest score with no arithmetic properties. We have known this for 30 years. The result: the ICER model resting on a cost-per-QALY value assessment is a complete nonsense. But yet ICER perseveres; the penny has yet to drop.

This is a point that should be understood by patient advisory groups. Rather than attempting to engage ICER, they should put ICER to one side and seek an alternative framework for evaluating therapy response for patients and caregivers in rare disease. ICER is a tiresome side show. Similarly, the focus should not be on QALYs; advocacy groups should drop this term. If quality of life is a critical outcome then there are other measures. These avoid the nonsense of creating imaginary claims.

The Way Forward

The focus must be on target populations in disease states. Rather than trying to apply a generic manifest score, where the evidence is for a small sample and inappropriate EQ-5D-3L utility in a rare disease state, we must abandon this charade in favor of a disease specific measure of quality of life, to complement disease specific clinical measures. We require feedback in real time to formulary committees, not imaginary claims that stretch 30 years into the future built entirely upon assumptions.

The proposed solution is for disease specific instruments that evaluate the extent to which the needs of pediatric patients, caregivers and adults are met (or improved) from the introduction of new therapies. We are not interested in non-evaluable claims that rest on the mistaken EQ-5D-3L calculus. ICER would deny any attempt to consider disease specific claims or to introduce patient centric, disease specific needs-fulfillment measures.

Manufacturer Responsibility

Manufacturers' should propose how their claims for the impact of new therapies in rare and chronic diseases are to be met. Are the claims to be purely clinical, or in recognition of the needs of patients and caregivers, should we broaden the claims framework to consider quality of life? Clinical endpoints are typically straightforward: the responses are on a scale which allows either interval or ratio measures. It is well validated and is accepted as central to clinical questions of therapy response. Moving beyond clinical to the more nuanced quality of life of patients and the caregivers requires instruments that accept the axioms of fundamental measurement. This acknowledges the importance of the social sciences, including the practitioners in health technology assessment, attempting to come at least part way to accepting the role of effective instrumentation and the standards of the physical sciences. We have a long way to go.

There are two main obstacles to the acceptance of the need for effective or accurate measurement: the ignorance of Rasch Measurement Theory (RMT) and the unwillingness to acknowledge 30 or more years of poor and possibly misleading measurement [2]. The latter creates problems for ICER and those focusing on the construction of imaginary cost-per-QALY worlds to create approximate information for formulary committees. The formulary committee will typically have no idea what they are talking about. ICER's claim to fame is the acceptance of its recommendations with the recipients having little or no appreciation of the value assessment model creating the imaginary claims.

Manufacturers and patient advisory groups can do better than this. If we are concerned to assess the impact of new therapies then we need, not some imaginary fantasy to support claims, but an evidence platform that can support claims assessment.

Not just Quality of Life

If we are to come to grips with therapy impact in quality of life terms then the question of measurement is paramount. Instruments which fail the elementary standards of the axioms of fundamental measurement must be discarded. Unfortunately, this means the majority of disease specific patient reported outcomes (PRO measures have to be rejected. They fail what has been known for the past 60 years as RMT standards. Whether this means they are just ignorant of these standards or prefer to ignore them and hope no one notices, is an open question. The fact is we have the standards and the techniques for instrument development that meet these standards. The end product in RMT is an interval scale with an index of response that can be subject to the typical array of statistical response tools.

This raises the question of the responsibility of patient advocacy groups. It is one approach to argue for the patient voice, it is another, and more complex approach, to put in place proposals specific to target patient groups in rare and chronic diseases for ensuring the patient voice, the needs of patients and caregivers, are accommodated in therapy evaluations. ICER will certainly be no help; they are off with the fairies in advocating the impossible application of multiattribute instruments to create impossible QALYS to support meaningless claims for product pricing and access. We need a hard-nosed reappraisal of the evidence gaps and techniques for meeting those gaps in target patient populations.

The Role of Formulary Committees

If health care systems are to assess the needs of patients in rare and chronic disease, then they have to take the lead. They may, of course, show not the slightest interest; in which case move to another health care system. For those who believe they have a duty of care, the formulary committee can set the required evidence standards for product pricing and access. Product placement and provisional pricing can be conditional on real world evidence feedback. Rather than an RCT, with its attendant time lines and costs (and lack of external validity) a well-structured observational study is an obvious solution. More particularly, if it is built on an existing registry structure then the task is made, potentially, that more straightforward.

Back to the Future

We have wasted 30 years in health technology assessment, not only in rare and chronic diseases but in all other disease areas by constructing imaginary worlds in the belief that evidence is created not discovered. Groups such as ISPOR have dominated the creation of imaginary worlds, committed to the belief that truth is consensus. Accepting claims is a sociological phenomenon. Hypothesis testing is rejected in favor of creating lifetime approximate information. Clams for formulary assessment, pricing and access have rejected not only the axioms of fundamental measurement but the concept of progress in the discovery of new facts that has been in place since the scientific revolution of the seventeenth century.

For ICER the voice of the patient is irrelevant. If it is considered, it is as a footnote; an obscure footnote which is seen as a minor yet annoying distraction. Attempting to establish claims or tracking therapy response in rare and chronic diseases is ignored. For ICER and ISPOR the focus, indeed the only focus, must be on generic multiattribute measures of utilities to drive mathematically impossible cost-per-QALY claims in all disease areas. Disease specific quality of life claims are anathema. Attempting to capture these would demonstrate how barren and unrewarding the current standards are for patients, physicians and caregivers. Perhaps we could reaffirm a commitment to real world and not imaginary world claims; the path not taken some 30 years ago.

REFERENCES

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