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DEPROGRAMMING THE RABBIT HOLE OF TECHNOLOGY ASSESSMENT

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ABSTRACT

The imaginary lifetime simulation model based claims developed by organizations such as the Institute for Clinical and Economic Review (ICER) are clearly pseudoscience. The recommendations driven by these models should not be considered, yet, virtually without exception ICER modeled claims are accepted at face value. The only defense is to respond to patients groups, notably in respect of disabilities, and forbid the consideration of QALYs in formulary decision making. This, unfortunately, overlooks the manifest deficiencies in the ICER modeled claims; deficiencies which should have been recognized as soon as ICER proposed its reference case. The fact that ICER has continued is a reflection of the lack of forensic skills among Medicaid formularies, even to the extent of neglecting expert review of ICER models by independent third parties with the appropriate skills. The situation is made the more tedious by the continued acceptance by groups such as the International Society for Pharmacoeconomics and Outcomes Research (ISPR) to promote the creation of approximate information while denying that hypothesis testing has a role of claims evaluation for pharmaceutical products and devices. This meme is dominant, a position held for over 30 years. Given the fact that, by the standards of normal science, the ICER modeled simulations and the creation of approximate information is pseudoscience, the question arises what steps, if any, should be made to extract technology assessment from this mythical rabbit hole. Should there be a concerted effort to point out the manifest deficiencies of the approximate information meme through deprogramming or recognize that, as in the case of conspiracy theories that proliferate in the US, the challenge is likely to fail. Rather than focus on the membership of ISPOR to deprogram, a more viable option is to focus on manufacturers and formulary decision makers. Perhaps, once these groups recognize the absurdity of ICER-type modeling, it will be put to one side.

INTRODUCTION

To a visitor from Mars (or any alien civilization of your choice) the extent to which formulary decisions in the US are based on imaginary rather than real world evidence must come as a surprise. After all, if the standards for normal science rest on real world evidence and hypothesis testing, as shown by the invention of science and the scientific revolution of the 17th , it seems somewhat perverse to throw this to one side and rely on approximate constructed information to drive formulary decisions for drug pricing and access [1]. Pseudoscience embodies statements, beliefs, or practices that claim to be both scientific and factual but in reality are incompatible with the scientific method; claims that are often contradictory and typically non-falsifiable [2]. Attempts rigorously to refute claims are denied by design, hypothesis testing is rejected while, all too often, the beliefs are adhered to by addicted adherents long after the claims have been effectively discredited.

Pseudoscience is not to be equated to conspiracy theories, although there are some interesting parallels. Pseudoscientific claims have a long and treasured history in the US, perhaps the most amusing being intelligent design. In health and medicine there are dozens of pseudoscientific claims, some potentially open to empirical evaluation; others defying that opportunity. Examples would include adrenal fatigue, colon cleansing, homeopathy, radionics, tin foil hat and reiki. To these must be added creating non-evaluable claims through simulation modeling for approximate information; which of course has the added bonus of allowing a multitude of competing models to generate non-evaluable and probably competing claims for specific products.

Unfortunately, in a situation reminiscent of the belief in conspiracy theories where the focus is on a cabal of illuminati directing events, we have some unfortunate statements regarding the role of 'leaders' in promoting the approximate information meme [3]. While it would be unreasonable to pursue the leaders responsible, it appears to be the case that the approximate information meme has not only support from academic centers but also journals such as the ISPOR house journal *Value in Health* and *Pharmacoeconomics*, but ISPOR guides to good pseudoscientific research practice and the buy-in from health service technology assessment groups such as the National Institute for Health and Clinical Effectiveness (NICE) [4]. Conspiracy theories, like the ICER models, resist falsification [5]. The confluence of pseudoscience and conspiracy theories is evident in the present COVID-19 pandemic. Not only do we have bogus therapies (think bleach) but widespread belief that the information on benefits and the supply of medications is controlled.

There is, however, a more insidious undercurrent to the belief in the construction of invented information to formulary decision making: relativism. If we accept the proposition that science is not an attempt to come to grips with reality, where evidence is never discovered, but always constructed within a particular social community. No one body of evidence is superior to another. The success of a 'scientific' research program depends not on its ability to generate new knowledge but its ability to mobilize the support of the community. Science is thus about rhetoric, persuasion and authority. This is the position of those thousands of adherents to the approximate imaginary information research program (if it can be called a program as is seems to be going nowhere). If all we have to look forward to are decades of ICER models, then we are in a weird position. Do we reject empirically evaluable claims and the discovery of new facts, or do we rest on our laurels and produce one more boring ICER evidence report. In fact not decades of ICER models: but hundreds of other models generating non-evaluable competing claims that can never be evaluated in the same disease area.

Unfortunately, this apparently perverse belief that creating modeled approximate information is of more import than a commitment to the discovery of new facts from a well-designed research program, puts any commitment to the scientific method to one side. In common with conspiracy theories, this approximate information meme (or paradigm) has the support of the majority of those in health technology assessment.

The purpose of this note is to consider whether or not this approximate information meme has any chance, at least in the near future, of being overturned. Is it possible to see those in health technology assessment committing to a meme that endorses the scientific method? Are we faced, as in the case of QAnon, with the task of deprogramming individuals who have blindly followed the approximate imaginary information meme over their professional lives and who are now faced with the prospect of the meme being relegated to a dumpster? Is there the prospect, as in the 17th century, of overthrowing established authority? Is this a genuine intellectual crisis or one that can be readily resolved or papered over? The case for deprogramming presented here is that the crisis is real and goes to the core of what we accept as health technology assessment. We are presently at an analytical dead end; a crisis 30 years in the making which has yet to be resolved.

A MEME FOR ALL SEASONS

Looking back over the past 30 years, one of the more intriguing aspects of health technology assessment is the commitment, not just in the US but globally, to the approximate imaginary, truth is consensus, information meme. This has been the dominant, if not the only, sanctioned approach to claims for comparative cost-effectiveness [6]. The origins of the meme and the devotion to it by leaders in health technology assessment, typically academic, have been explored in other commentaries. The key is to understand, in the early 1990s with the advent of health technology assessment guidelines, the options facing decision makers; or at least those wishing to carve out a technology assessment niche, were clear cut. Faced with a dearth of information other than data from pivotal trials at product launch,, the options were: (i) to recommend the commitment to a long term research program to fill evidence gaps and report back to formulary committees on product comparative performance; or (ii) to recommend the creation of evidence for comparative product performance through assumption driven simulations to create approximate (and non-verifiable) claims. The former could be judged pedestrian and time consuming; the latter was attractive to those looking for a short-cut where models could replace real world evidence. In the background, of course lurked the consulting opportunities that imaginary models could generate; a marketing strategy underwritten by manufacturers. After all, a cynic might describe it as a win-win strategy: create lifetime simulations that could never be tested other than by a challenge to assumptions – which could easily be brushed off.

The obvious weakness in this 'all seasons' strategy was the opportunity to inundate the market place with competing models to create competing claims; models that could be tailored to yield promised results with reverse engineering assumptions and creating probabilistic sensitivity analyses to support the clients product for the less discerning formulary committee. How could one model or a modification of that model be given the good housekeeping seal of approval? The response was to be expected. In single payer health systems such as the National Health Service in England limits were placed on imaginary modeling standards with a single referee to appraise the merits (not the 'truth') of modeled claims [7]. Indeed, while it may seem ridiculous, 'academics' became specialized in the evaluation of imaginary worlds, challenging assumptions and even producing their own models. Perhaps ISPOR should have invested in a fantasy pharmacy novel series; Narnia redux.

While the UK avoided an 'open season' for competing models, the US with a fragmented health system was a prime target for competing models; aided by the fact that none of public and commercial health systems made any attempt to set model formulary submission standard that reflected the standards of normal sciences. At best the Academy of Managed Care Pharmacy entered the fray with a recommended yet flexible set of formulary guidelines but without recognizing, not only the standards of normal science, but that there were no forensic skills in place with state Medicaid and other formularies to evaluate the competing models [8]. A situation made all the more bizarre when those few with some forensic skills subscribed to the imaginary information meme. The more substantive critiques of modelled claims were unrecognized. ICER's contribution to this scene was to argue that it occupied a unique place as a self-proclaimed independent arbiter; a model builder who would ensure certain standards were met in approximate imaginary information model building and that its review of modelled claims for product pricing and access to pharmaceuticals would serve as a NICE-equivalent. Unfortunately, ICER also subscribed to the approximate information meme and, despite arguments presented, steadfastly refused to budge from its belief in modeled claims and the irrelevance of the standards of normal science in health technology assessment.

ICER has, however, shot itself in the foot. In November 2020 it released its modelling cloud platform, ICER Analytics [9]. This allow, when complete, access to all of the models developed for ICER evidence report so that, with a backbone ICER model, assumptions can be changed and ICER's claims challenged. I`CER has thus opened the door to competing models which, with the claim that they are based on a 'core' ICER structure, could potential confuse Medicaid and other formularies. A situation which would be exacerbated by their absence of forensic skills.

THE FORCE OF BELIEF

Rational argument and facts are unlikely to challenge belief. In the case of conspiracy theories, their ready acceptance reflects our in-built willingness (even need) to impose structure and recognize patterns – even where are none. In technology assessment we impose structure in simulation modeling using a reference case guidebook. A causal structure is imposed linking limited clinical data points through assumptions to create a claim for cost-effectiveness. A claim which is patently absurd if for no other reason that the links in the causal chain, the creation of QALYs from multiattribute ordinal utility scores, is mathematically impossible [10].

Yet, even if these errors are pointed out, practitioners persevere in their belief, passing the belief on through what Dawkins describes as memetic transmission fidelity to new acolytes. One obvious reason is peer pressure. As members of a group we require social acceptance, resisting external pressures for change. If the group (it may be your professor in a graduate class) accepts a belief, then you are unlikely or at least unwise to challenge that belief. The more widespread the belief in simulation models, the more likely you are to be believe and emulate the model builders worldview. You believe it is true; truth is consensus. Your academic career in technology assessment, creating evidence from imaginary constructs begins. Welcome to fairyland. It is unlikely that ISPOR, for example, will announce a damascene conversion and reject the I-QALY along with its decades long commitment to impossible

imaginary information. The most plausible scenario is that ISPOR and its house journal *Value in Health* will gradually phase out reference to I-QALY and simulation models, but without unduly alarming its membership and readership. ICER is in a somewhat more delicate situation as it has a well-documented trail of deniability and false claims [11]. Responses to public comments on draft evidence reports. ICER simply refuses to believe that their simulations and claims are pseudoscience. A cynic might observe that the ICER reference simulation is defended because it is the core of the ICER business case; revenue drives acceptance. Unfortunately, the truth is more concerning: ICER and its academic supported really believe in the construction of imaginary claims and approximate information in decision making; they are deeply in the rabbit hole.

DEPROGRAMMING BELIEF IN SIMULATED TECHNOLOGY ASSESSMENT

After 30 years, it is a challenge to envisage how the imaginary simulation meme (or paradigm) is to be overturned. Deprogramming those with a pathological belief in conspiracies has achieved a singular urgency in the post-Trump era. Whether it is even possible to bring them 'out of the rabbit hole' is problematic with many psychologists taking the view that it is virtually impossible. Without being overly sensational, the challenge facing those wishing to overturn the approximate information through imaginary constructs belief in health technology assessment face similar challenges. After some 30 plus years of a constant reinforcement of the imaginary worlds meme the belief is well entrenched. After all, academic thought leaders have assiduously promoted and appear deeply committed to the approximate information belief supporting subplots such as probabilistic sensitivity analysis to bolster the semblance of relevance to decision makers.

Faced a with a reasoned critique of the failure by model builders to meet the standards of normal science, criticisms are simply brushed off; ICER, for example, continues to believe that multiattribute utility scales are defensible 'single' attribute ratio scales yet acknowledge at the same time that the scale has negative utilities [12] [13]. One answer is that, with conspiracy theorists, they can hold to contradictory beliefs at the same time: the defense is 'the jury is still out'. Or, to paraphrase Tertullian and, later, Sir Thomas Browne "I believe because it is impossible"; political and social ideas that cannot be tested by evidence tend to have a stronger psychological advantage.

A key maxim in deprogramming weird beliefs is not to be confrontational. Perhaps, attempting to explain that claims based on lifetime simulation models fail the standards of normal science, or lack a certain *je ne sais quoi* are too challenging: first, the recipient has probably never been exposed to these standards and is at a loss to explain the demarcation test between science and pseudoscience; second, the recipient has probably never been exposed to the notion that there are axioms of fundamental evidence; and third, the recipient has probably never been exposed to the standards for dimensional homogeneity in creating single attribute measures. This sheer ignorance is compounded by the fact that it is not the academic model builder who subscribes, possibly unwittingly, to untruths but the recipient of the modelled claims who is equally in the dark of the rabbit hole. The conspiracy theorist has a ready audience.

The issue of deprogramming casts a different light on paradigm shifts and the acceptance by the majority of participants that the world has changed. After all, few disputed Einstein's special theory of relativity and its role in accommodating and enhancing Newtonian mechanics. The transition was 'smooth'. This is unlikely to be the case with technology assessment where so many careers, unlike with the acceptance of Newtonian mechanics, have been built on a methodology which, even at inception, defied accepted standards for normal science. There is not the question of embracing a pre-existing paradigm into a new paradigm, but of rejecting completely the prior paradigm as nonsense. Too many careers and accolades rest on this nonsense. There are unlikely to be statues erected in the halls of academe for 30 years in a rabbit hole. A more appropriate analogy might be to the Lutheran reformation and its attack on centuries of Catholic belief.

As evidence for the strength of belief, consider the multiattribute utility instruments. Attempts to prove and publish reasoned critiques have all too often failed. Yet by the standards of the physical science they are clearly illegitimate constructs. They fail to meet the axioms of fundamental measurement (these were never considered), they are the creation of clinicians who consider quality of life to be defined entirely in clinical terms (perfect health for the EQ-5D-3l/5L instruments is where you report no problems on five symptoms: mobility, self-care, usual activity/pain discomfort, anxiety/depression). This is meaningless, not only because the symptoms may have no relevance to individuals in a disease state, but that aggregating of these five symptoms (or attributes) is meaningless as it fails to develop a measure which is unidimensional or dimensionally homogeneous. In terms of measurement theory, these are only ordinal scores [14]. This means that attempting to utilize these score to create QALYs is mathematically impossible. ICER has denied this with its academic modelers believing that the EQ-5D-3L and other multiattribute utility scores not only have interval properties but are actually ration scales in disguise. Even the most widely used textbook in technology assessment admits that the fact that multiattribute scales yield negative values means that they are not ratio scales yet falls back on the somewhat confused argument that as they are interval scales (which they are not) they can be used to create ratios and thus QALYs.

OUT OF THE RABBIT HOLE

What's remarkable is that the 30 years the leaders in the field have spent promoting imaginary simulations has also witnessed and entirely different approach to evaluating quality of life, not to mention ample warnings over the implications of a failure to recognize the limitations imposed on quality of life claims by the axioms of fundamental measurement. There are two key arguments: first, quality of life should be a patient centric, single attribute measures that capture the needs of patients and how those needs are met by therapy interventions (which can be complemented by clinically focused single attribute measures) [15]; and second the acceptance of the standards of normal science focusing on empirically evaluable claims

Accepting these is no walk in the park. It requires a rejection of approximate (or impossible) information in favor of a worldview that is disease and patient focused [16] [17]. Needs are defined for target patient groups. After all, therapies are focused on patient groups; trials employ inclusion and exclusion criteria

to define the target groups. We have the tools to assess that response; indeed, these tools have been available for the past 60 years with the recognition of the contribution of Rasch Measurement Theory (RMT) [18].

RMT presents a major obstacle in deprogramming. It is never mentioned in the technology assessment textbooks or in ISPOR programs to introduce its members to health technology assessment. RMT is the key to overturning the approximate simulated information program. It rests on a simple premise: measuring response to therapy (or performance in any test or game) must accommodate the ability of the patient to respond to an item and the difficulty of item response. The probability of success, for example, in a high jump reflects the ability of the athlete and the height of the bar. If ability exceeds the difficulty of the jump then the probability of success increases. RMT transforms ordinal level data to interval level measures. It is the only way an interval scale can be constructed for latent attributes such as needs based quality of life.

Unfortunately, the rabbit hole is a lot deeper than many would appreciate. Certainly, part of the architecture of the hole is described by ordinal multiattribute utility scores but the 'cancer' is metastasized: with few exceptions the hundreds of disease specific measures that have been promoted over the past 30 plus years also fail the RMT standard. They are multiattribute ordinal scores. The primary reason for this is that the developers were unaware of the axioms of fundamental measurement and the need to create an interval score for singles attributes. Created primarily by clinicians, they assumed that a single score could be generated by adding values from, for example, Likert scales for selected symptoms. Raw data are not measures. RMT provides the means to produce genuine interval measures.

What has to overcome is the sheer unwillingness of practitioners in not just health technology assessment but the wider social science arena to entertain the notion that raw data are not measures. To admit this is to open literal Pandora's Box of accumulated nonsense. Many have much to lose. Even so, ignorance of measurement theory is no defense. More egregious is the rejection of the standards of normal science that embody a commitment to the axioms of fundamental measurement.

DEPROGRAMMING OPTIONS

Moving on from a discredited meme is difficult; with so much invested in the creation of approximate imaginary information, where the term approximate is meaningless, it is doubtful if any substantive change will be entertained. Indeed, given the inherent absurdity of the value claims and the irrelevance of the analytical framework, it may not be worth the effort. There are too many layers of belief, in many ways a global acceptance with the professional standing at risk for so many. By the same token, attempts to discredit the 'facts' and 'inconsistencies' of conspiracy theories also meet a brick wall.

On a more positive note, the authority of leaders in health technology assessment can only be maintained if there is an audience for their modeled claims. If the audience judges the claims to be irrelevant in the process of formulary negotiations for pricing and product access, let alone as a basis for

value contracting, then the theater is empty. There is no audience. This is no so much the fact that the framework is judged pseudoscientific but that, possibly more galling, it is simply judged inconsequential.

At the same time the rejection of approximate information opens up the opportunity for a new value assessment framework; one that accepts the standards of normal science, including fundamental measurement, to support credible product claims that are empirically evaluable and replicable. A framework which emphasizes the necessity for single attribute claims, the provisional nature of pricing faced with the potential discovery of new facts through long-term evidence bases (e.g., registries) for target patient populations. This puts the focus on the demand, or market for, health technology assessment claims. If groups such as commercial and public sector formulary managers accepted the need for a research program to assess claims for products, perhaps supported by value contracting, then ICER would cease to have an audience for its imaginary model recommendations. There are a number of instances where the QALY is not accepted as support for pricing and access negotiations. While this reflects concerns over equity in QALY measures, notably in disabled patient groups, a more substantive argument can be made to reject any claims based on ICER type models. This applied in particular to value contracting where the contract is only feasible if claims are empirically evaluable, meeting required evidence standards. This implies an evidence base to track product performance and the choice of both single attribute ratio and ordinal outcome measures.

Although only recently released, the framework for formulary submission standards has been proposed in Version 3 of the Minnesota proposed formulary guidelines. These reject imaginary simulations. Emphasizing instead the role of single attribute claims supported by protocols describing how these claims are to be evaluated and reported to a formulary committee [19]. All claims must conform to the axioms of fundamental measurement with the interval scale as the key element in evaluating response to therapy.

CONCLUSIONS

Whether a belief is considered outside the standards of normal sciences is, for many in health technology assessment, irrelevant. Too many people believe that truth is consensus. For 30 years a network of practitioners has driven this ‘false’ narrative. A belief system that has been endorsed globally by health assessment agencies in multiple countries, by academic institutions, by guidelines issued by groups such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and with ISPOR membership surveys showing a complete commitment to such a modeling strategy. Just as the GOP is now the party of Trump (or QAnon) so the field of health technology assessment is dominated by approximate (or impossible) information to support claims for formulary decisions. This is a ridiculous situation.

A case can be made that, deliberately, these delusions regarding imaginary simulations were designed to fend off criticism. The enthusiastic endorsement of modified scenario claims, the application of sensitivity analysis and probabilistic likelihood estimates all seen designed to create a fog to fend off criticism. If enough people subscribe to a belief, that belief must be correct irrespective of evidence to

the contrary (e.g., intelligent design) There is no appeal to evidence (or even logic); only to the ability to modify assumptions and produce competing scenarios without challenging their belief in the core model.

The point that is missed is the appeal to evidence that is the core of the scientific revolution. More destructive, there is the relativistic belief that science is not a way of coming to grips with reality. Evidence is always constructed; it is never discovered. Evidence is always constructed within a social community: a description that applies to those subscribing to imaginary approximate claims in health technology assessment. There is no research program that is evidence focused; a research program that focuses on generating new knowledge. Unfortunately, to the denizens of the rabbit hole, knowledge is based, not on evidence, but on rhetoric, persuasion and authority.

Is it possible to deprogram such a constellation of beliefs? At each stage of model development we can point to a failure to respect the standards of normal science. We cannot engage in language games to claim there is no external reality. Can we argue that what we see is not really there? Galileo would be amused. Our language must not define the limits of our world. The most telling argument against the model simulation paradigm is that it is an analytical dead end; just as conspiracy theories have no basis in reality, so the modeled claims fail the simple standard set by the standards of normal science; propose claims that are credible, evaluable and replicable.

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