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VALUE CLAIMS AND THE NEW START IN RARE DISEASE FORMULARY SUBMISSIONS

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Abstract

Rare disease presents a number of challenges to formulary committees and health system decision makers, not least the absence of a viable assessment framework to establish value claims for the product to support both preliminary pricing and access decisions as well as ongoing relations between the manufacturer and the formulary committee and health system. Current analytical frameworks for health technology assessment and, more specifically, economic evaluations to support claims for cost-effectiveness in rare disease are actually a barrier to understanding the benefits of rare disease therapies. While this conclusion applies across the board to all disease states and the introduction of new therapies, it has a particular resonance with rare disease given the limited evidence at product launch and the temptation to construct assumption driven simulation models to invent evidence; a vain and foolhardy attempt to meet evidence gaps. The purpose of this brief commentary is to show conclusively that the current belief system in technology assessment is an analytical dead end; one that raise unnecessary obstacles to the timely acceptance of new rare disease interventions allied to often absurd demands for price discounting and controls of therapy access. The NEW START formulary submission guidelines put the current analytical framework to one side in favor of one that actually recognizes the standards of normal science and the role of fundamental measurement. Rather than attempting to come to some overall assumption driven imaginary conclusion that a rare disease therapy at recommended pricing points has a high probability of being cost-effective, NEW START proposes a return to the standards long held in the physical sciences that all value claims must be credible, evaluable and replicable. This means, in conforming to the axioms of fundamental measurement that all claims should be formulated as unidimensional, single attributes with ratio or interval measurement properties. Value claims, whether they are for clinical endpoints, patient reported outcomes (PROs), drug or resource utilization, must meet these standards. There is no interest in ersatz claims for imaginary cost effectiveness, but on credible claims support by evaluation and reporting protocols to support provisional pricing and access decisions. One-off modelled economic evaluations are rejected in favor of the discovery of new, yet provisional facts; a process that should continue for patent life or the life-cycle of the product. There is no other option unless we simply put the discovery of new facts in rare disease in the too hard basket and fly by the seat of our pants.

INTRODUCTION

The single most important barrier to the adoption of rare disease therapy interventions is the current health technology assessment belief system, that has been based for the past 30 or more years on the role of approximate information to support decision making in health systems. Any notion of

the standards of normal science is absent. Rather that recognizing the role of establishing credible, evaluable and replicable claims for therapy evaluation, the belief holds that the only valid approach is to construct approximate, imaginary information claims through assumption driven simulations. This is seen as an effective response to situations where, at product launch, information on the therapeutic benefit of a new therapy is limited. Rather than support an ongoing research program to discover new, yet provisional facts, the modelled simulation is an effective substitute.

The NEW START formulary submission guidelines are well suited to the evaluation and acceptance of rare disease therapies [1]. The focus on value claims means the welcome ability to dispense with modeled simulation approximate information claims; a rejection driven primarily by the fact that there is a framework that supports value claims that meet required standards.

Certainly, we can point to a number of characteristics of rare disease that have to be accommodated in rare disease formulary submissions and an ongoing engagement between manufacturers and health systems. These include: (i) an analytical framework for rare disease proposals that is robust and flexible; (ii) a comprehensive assessment of the demographic, social and resource utilization characteristics of the target patient population; (ii) establishing algorithms to capture the target patient population; (iv) an assessment of unmet medical and evidence needs; and (v) existing registries; (vi) systematic reviews for response to therapy; and (vii) capturing the patient and caregiver voice in terms of needs-fulfillment. These should be covered in the review of the target patient population to support value claims are as part of the formal formulary submission.

THE FAILURE OF TECHNOLOGY ASSESSMENT

The current belief system (or meme) for health technology assessment, sometimes referred to incorrectly as economic evaluation, is bankrupt [2]. For 30 years leaders in the field and their many followers, including national single payer gatekeepers, have convinced themselves that we can reject hypothesis testing, including structured research programs, in favor of constructing assumption driven lifetime simulations to invent cost-per-QALY incremental claims to support formulary decisions [3]. This presents a major challenge and disservice to new therapies entering the market place, but as a barrier to acceptance has a particular resonance for rare disease. Indeed, we can argue that this analytical framework is the principal barrier to the provision of new therapies in rare disease for target patient populations.

This approximate information analytical framework, as applied by ICER has been shown conclusively to not only deny the standards of normal science but the axioms of fundamental measurement [4]. The argument is straightforward and starts with Hume's problem of induction First introduced in 1748, the issue is easily stated: the future is unknown and the fact that past futures have resembled past pasts does not mean that future futures will resemble future pasts[5] it is illogical to attempt to create a simulation model based upon any notion of the realism of assumptions; assumptions as to the future can only be defended by the psychology of the analyst.

The failure of the current technology belief system goes even further: the focus on the mathematically impossible QALY [6]. As the preference scores created by the various multiattribute instruments are ordinal, the QALY is a mathematically impossible construct. This means that any analysis based on the QALY is also redundant. This means we must reject invented claims for

incremental costs-per-QALY outcomes and, by the same token, cost per QALY thresholds which have been the bane of rare disease simulations. The fact that rare disease therapies are expensive is not unexpected; it is a disservice to suggest, even with higher imaginary cost-per-QALY thresholds to still recommend substantial price discounts and limited access recommendation. Imaginary non-evaluable claims should not trump evaluable value claims.

NEW START ends these practices; the focus is on specific evaluable value claims that can support contract negotiations for provisional pricing, while still holding manufacturers to these claims. At the same time, NEW START recognizes the need to meet the standards of normal science and fundamental measurement.

NEW START PREMISES

The NEW START formulary submission package, which applies across all disease states and not just rare diseases, rests on two premises:

- 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.

Unless individual value claims meet ratio measurement standards (with a true zero) they cannot be bundled together. The formulary submission is, therefore, a profile of individual value claims that capture clinical, patent reported outcome (PRO), drug and resource utilization elements that are separately evaluated and reported to the formulary committee or health system. Each has the possibility of being reassessed, with additional value claims considered, this makes more robust the evidence based for continuing engagement between manufacturer and formulary committee; modeled approximate information simulations to create imaginary blanket claims for cost-effectiveness have no place in the NEW START.

A STRUCTURED RESEARCH PROGRAM

Rather than relying on one-ff assumption driven simulations, the focus of NEW START is on supporting a structured research program to meet evidence gaps and the discovery of new, yet provisional facts; a focus of particular relevance to rare disease. The bread and butter of normal science for 300 years; or, to put it is modern terms, a process of conjecture and refutation. Science is an evolutionary process driven by its focus on discovery and appeals to superior evidence [7] . measurement is critical; if we cannot measure, we cannot seek out new facts, this is why in rare and other disease we must ask the question as to the relevance of present analytical techniques.

This process must begin in the development phase of a proposed new rare disease therapy. Manufacturers should be aware of the limitations, or more properly, the irrelevance of the current system for creating imaginary cost-effectiveness models in rare disease based on limited evidence to drive 'realistic' assumptions, with any shortfall in the assumption department conjured up.

If value claims for rare disease interventions are to be coherent, then they must begin with a detailed assessment of the target patient population focusing on the anticipated indication for the therapy. The parameters of this assessment will be to identify the core value claims anticipated for the target patient population and the gaps that could usefully be met as part of the development process. Of particular relevance here would be the patient and caregiver voices, given the possibility of a pediatric indication and the need for support over the patients' lifetimes with existing standards of care. There are well established techniques that capture the patient voice (but not for pediatric patients themselves) and those of caregivers with application of Rasch measurement Theory (RMT) or Modern Measurement Theory (MMT) [8] . A recent example of the RMT/MMT application is the needs-fulfilment adult measure for neurofibromatosis type-1 associated with plexiform neurofibromas (PlexiQoL) [9].

At the same time, the assessment must focus on the current standard of care reflected in drug utilization and resource utilization. These cannot, as with the patient and caregiver voices, be left to the last minute. Data for rare disease populations can be limited and dispersed with the, often limited number of patients involved. If a structured research program is envisaged then part of that program will involve value claims for therapy impact of drug and resource utilization following marketing approval. At the same time, there may be an opportunity

Data collected in this assessment or profile of the target population are not intended to support developing an assumption driven simulation to create imaginary outcomes. Indeed, in the US, it would be advisable not to correspond with icer if that organization is proposing an evaluation of the therapy with recommendations for pricing and access. any requests to become a stakeholder can be easily deflected by pointing to the irrelevance of the icer analytical framework. A message that can be taken to formulary committees and health systems. to support claims for a NEW START core value claim analysis. 'estimates' as part of the formulary submission.

THE NEW START SUBMISSION

Prior to product approval, the manufacturer should have established what it considers the core value claims for the product. A convenient classification is to consider them under four categories: (i) clinical value claims; (ii) patient reported outcomes (PTOs); drug utilization; and (iv) resource utilization. Apart from the issue of a PRO, all other value claims would be selected to have ratio properties.

As already noted, the PRO must have interval or, if possible, ratio properties. This effectively eliminates all generic multiattribute instrument (so QALYs are excised) and the majority of disease specific PRO measures as they typically are ordinal scores and hence fail to capture response to therapy. All that we have left are instruments that meet RMT standards: the unidimensional single attribute need fulfillment measures which have interval properties and can be transformed to bounded ratio scales. Unfortunately, as these are by definition disease specific the manufacturer

will have had to decide whether or not to invest in constructing one for patients and/or caregivers in the rare disease target patient population. This should have been an early decision in product development, but can set the rare disease state apart in meeting RMT or MMT standards for need fulfillment quality of life and the impact on it of the therapy intervention. The bounded ratio scale can, of course, support the equivalent to a QALY (described as the N-QoL) [10] . One option open to the manufacturer is to specify a value claim in terms of developing a needs-fulfillment instrument, but that would detract from the value claim case presented to support initial and provisional pricing and access negotiations.

The NEW START guidelines propose a two-stage process to assess the relevance to the health care system of proposed value claims (or core value claims). Once the evaluation of the target population has been provisionally completed and potential value claims identified, then discussion should be held with health systems to justify the proposed value claims and their role in longer-term engagements as inputs to a national research program. A key consideration is feedback on the relevance of the value claims to supporting provisional pricing, access and potential contractual arrangements. The intent is that value claim, both those proposed from pivotal clinical trials and those proposed for ongoing evaluation are the basis for pricing and access decisions.

If a needs-fulfillment instrument has been developed (or is available) then the manufacturer should give consideration to this as part of the pivotal trial protocols as the appropriate measures of quality of life; a measure that meets all required standards. This would be a significant counterweight to approximate information modeled claims which have attempted to identify and apply multiattribute preferences and QALYs to establish pricing points for imaginary cost-effectiveness claims. This would place the patient and caregiver voices front and center in negotiations with health systems and as a major rebuttal to ICER should it presume to undertake an imaginary appraisal.

PROTOCOLS

All value claims submitted to a formulary committee or health system must be supported by a protocol detailing how the claim is to be evaluated and reported. This is, of course, little different from the protocols recognized to drive randomized controlled trials (RCTs) And observational studies. The difference is that a value claim respects the condition that any claim, even if supported, is only provisional. All we can say is that the claim has not be falsified but still subject to further assessment as part of a structured research program. The protocol links the value claim to the evidence to evaluate the value claim and report, in a meaningful timeframe, to the formulary committee or health system. Each protocol could be agreed as part of the submission process with, if required, a contractual agreement. The manufacturer, to keep costs to reasonable minimum, should attempt to have a common set of value claims to report across all health systems.

Given the nature of rare disease, with the preponderance of genetic causes, a long-term research program supported by the manufacturer is essential. The evidence base could be, obviously, a registry to support a core set of value claims to be reported to all participating health systems. This would be ongoing with the focus on the response, durability of response and need fulfillment for patients and caregivers.

Value claims, as noted above, apply not only to therapy response and needs-fulfillment, but to drug and resource utilization. The NEW START proposal is not focused on costs but on agreed categories of drug utilization and resource use. These would be identified as part of the initial review of the target patient population, identified by appropriate codes (CPT, NDC) and the proposed databases for tracking and reporting. Putting aggregate cost claims to one side follows from the importance of value claims that are empirically evaluable. Target drug and resource use will be reported to the formulary committee, including if appropriate compliance behavior. If the formulary committee or health system wishes to apply unit costs that is just part of the negotiation process.

CONCLUSIONS

Manufacturers, particularly in rare disease, cannot wait until the last moment to engage with formulary committees and health systems following an invitation to make a formulary submission. Following NEW START recommendations, preparations should start considerably earlier to ensure a comprehensive review of the target patient population to support value claims proposals and the preparation of protocols to support those value claims. Unless mandated by health systems, typically outside of the US, manufacturers should not engage in building assumption driven simulation models, or become a 'concerned' stakeholder with ICER. If manufacturers are asked why they have put approximate imaginary information to one side, the case can be readily made that it is in no one's interest to base formulary decisions on imaginary non-evaluable claims that fail the standards of normal science and fundamental measurement.

Given the nature of rare disease and, in most cases, the potential lifetime impact of new interventions, manufacturers should commit to an ongoing research program to support disease area and therapeutic class reviews. Formulary approval is not a one-shot effort; unlike the current belief system endorsed by ICER, the focus must be on a robust evidence base to support an ongoing engagement with the target patient population by the manufacturer. Data at product launch are obviously limited; this is recognized but is effectively countered by commitments to ongoing value claim assessments.

NEW START is new, yet not new. Certainly, in rare disease there have been negotiations and contracts to support 'spread' pricing proposals based on response to therapy over a few years following product launch. Where NEW START differs, apart from rejecting imaginary modeled claims as both barriers and analytical dead ends, is the focus on a profile of value claims driven by protocols that set the stage for an ongoing engagement between the manufacturer and the various formulary committees and health systems; value claims which are designed to be empirically evaluable, supporting ongoing provisional pricing negotiation driven by the discovery of new facts in therapy response.

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