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## Imaginary Worlds: A Systematic Review of the Status of Modeled Cost-Effectiveness Claims Published in the *Journal of Medical Economics* from January 2015 to December 2015

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### Abstract

*The purpose of this review is to evaluate the credibility of modeled claims for cost-effectiveness studies published in the Journal of Medical Economics (JME) in the period January 2015 to December 2015. Credibility is assessed in terms of the standards of normal science. Are the claims made capable of falsification and replication? Following the PRISMA-P recommendations, abstracts of all papers published in the JME were evaluated by both authors independently against a MeSH terms checklist: cost, cost-effectiveness, cost-utility, outcomes, QALY and Markov. A total of 32 studies were identified. A systematic review of each study was then evaluated. The consensus was that all studies be included in the review. Each study was judged against four criteria: (i) Is the model capable of generating evaluable claims? (ii) did the author(s) attempt to generate evaluable claims? (iii) did the author(s) suggested how the claims might be evaluated? and (iv) did the author(s) caution readers as to the implications of generating non-evaluable claims for the credibility of the analysis? None of the studies presented their claims or projections in an evaluable form and none suggested how they might be evaluated. None met the standards of normal science. The claims made for cost-effectiveness were either impossible to verify, or if potentially verifiable, were not presented in an evaluable form. The studies lacked credibility. There was no basis for assessing whether the claims were right or even if they were wrong. The JME is not alone. As part of an ongoing systematic review program, covering the leading journals and focusing on chronic condition areas, it is clear that the majority of cost-effectiveness papers also fail the test of credibility. Of course, it might be that the consensus opinion among practitioners is that non-evaluable projections are acceptable. Evidence is not discovered, but is constructed through models and simulations. This lack of scientific credibility is a major concern. If medical economics is to advance through the formulation and testing of hypotheses, then editors of journals should consider whether or not to set standards for the acceptance of publications to include the requirement for evaluable claims and the results of claims assessment. If this is not acceptable, then it should be made clear that published papers are simply imaginary worlds or thought experiments.*

**Keywords:** cost-effectiveness modeling, credibility, imaginary worlds, scientific method

### Introduction

In a recent supplement to the *Journal of Medical Economics (JME)*, the case was put forward that if claims for the impact of products and devices on costs and outcomes in health care systems are to be accepted, then they should meet the standards expected in 'normal science'<sup>1 2 3 4 5</sup>. The argument was made that if modeled claims are to be credible, practical, and useful in formulary decisions, then the only acceptable modeled claims in formulary submissions are those that are evaluable in a timeframe relevant to the needs of a formulary committee. If claims do not meet this standard, they should be rejected. Given the experience of modeled claims made to the National Institute for Health and Care Evidence (NICE) in the UK, the current situation in the US, and other developed economies, a new research agenda was proposed. This

agenda would focus on the evaluable impact of products and devices on patient outcomes, resource utilization, and the costs of health care delivery. Central to this research agenda would be the recognition that unless a modeled study yields evaluable claims that are reproducible across multiple healthcare settings, the model has no credibility when set against the standards of normal science. There should be an acceptance that the standards of normal science apply to the process of discovering new facts in health care decision making<sup>6</sup>.

The purpose of this systematic review, which is part of a program being undertaken at the College of Pharmacy, University of Minnesota to evaluate the credibility of cost-effectiveness claims in leading journals and in chronic conditions, is to assess cost-effectiveness claims published in the JME during 2015. A review of papers published in *Pharmacoeconomics* during 2015 has ready been published<sup>7</sup>. As detailed in the *PharmacoEconomics* review, if a modeled cost-effectiveness claim is to meet the standards of normal science then it has to (i) involve the construction of an empirically evaluable coherent theory and (ii) facilitate the testing of hypotheses through experimentation or

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observation. These are standards that have been in place since the 17<sup>th</sup> century and demarcate science from pseudoscience; the demarcation between natural selection and intelligent design<sup>8</sup>.

The purpose of these ongoing reviews is to determine whether published studies meet the standards of normal science or whether they reflect a relativist position that, through consensus, believes other standards should apply in supporting value claims for pharmaceutical products and devices<sup>6, 9, 10</sup>. It is not the purpose of the research program to deny constructed modeled or simulated claims. Rather, in focusing on the claims, irrespective of the perceived merits of the model or simulation generating those claims, if they fail the standards of falsification and replication, then they are not credible inputs for health care decision making<sup>11, 12</sup>. The standards of normal science are absolute. Constructed evidence and untestable projected claims are not acceptable.

### Methods

Following the PRISMA-P recommendations, abstracts of all papers published in the *JME* in the period January 2015 to December 2015 were evaluated by both authors against a MeSH terms checklist: cost, cost-effectiveness, cost-utility, outcomes, QALY and Markov<sup>13</sup>. A total of 32 studies were identified. Each study was then carefully reviewed and evaluated. The consensus was that all studies be included in the review. (see references 22 through 53).

Four questions were considered in the assessment of whether the modeled cost-effectiveness studies presented met the standards of normal science:

- Is the model capable of generating evaluable claims?
- Did the author(s) attempt to generate evaluable claims?
- Did the authors suggest how the claims might be evaluated?
- Did the author(s) caution readers as to the implications of generating non-evaluable claims for the credibility of the analysis?

An evaluable claim was defined as one that had the potential to be assessed empirically in a timeframe relevant to the needs of a formulary committee (ideally a period of 2 to 3 years). This period was chosen because a evaluable claim was seen as provisional; a point that was made over 10 years ago in formulary guidelines proposed for WellPoint Inc. (now known as Anthem Inc.) in the US<sup>14</sup>. A product or device would, following these guidelines, be accepted by a formulary

committee for formulary listing, but subject to an agreement with the manufacturer to report back to the committee with evidence to support the claims made. There was no restriction on the type of claim. These claims could be for product comparative effectiveness, for the impact of the product on resource utilization or some combination of these to support a claim for incremental cost-effectiveness. The claim for comparative effectiveness could encompass clinical endpoints as well as those captured as patient reported outcomes. Irrespective of the claim made, this was assessed in the context of the claim providing feedback to a formulary committee to support ongoing disease area and therapeutic reviews.

If these credibility standards are accepted, then the responsibility is on the authors of a modeled claim or simulation to structure their analysis to generate evaluable claims. If claims are put in cost-utility terms, then it has to be shown how those claims might be evaluated. If claims are expressed in adverse events avoided or if the claims were disaggregated by a base-line risk of stroke, again it should be shown how those claims are to be assessed.

In judging whether or not a model might support evaluable claims, even if the possibility is not considered by the authors(s), three characteristics of a model are important. These are: (i) the modeling framework, (ii) the choice of primary outcome measure; and (iii) the time frame for the model. A Markov or discrete event simulation model with a lifetime perspective and with discounted cost per quality adjusted life year (QALY) claims as the primary endpoints would be one that would be impossible to evaluate. Against this, a simple, trial-based decision model with a timeframe of 12 to 18 months with claims expressed in clinical terms (including PROs) and resource utilization endpoints would, given access to readily available data sources in the US, be open to hypothesis testing, feedback to a formulary committee and replication in other target populations.

The important point to note is that a modeled claim is not to be judged on the reasonableness or otherwise of the assumptions of the model. Certainly the model would be expected to cover comparator products, or least the key comparators, and to identify the target population for the claims. The NICE reference case model is of particular interest<sup>15</sup>. The reference case is important in health technology assessment because it has been adopted as the preferred format for formulary submissions in a number of single payer health systems<sup>16, 17</sup>. It has also influenced in the US the Academy of Managed Care Pharmacy (AMCP) *Format for Formulary Submissions*<sup>18</sup>. Through standards established by professional groups such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the

adoption of quality check lists such as CHEERS, the reference case standard has had a significant effect on the widespread adoption of constructed, lifetime cost-per-QALY models to generate non-evaluable claims for product performance<sup>19 20 21</sup>. This acceptance is such that cost-per-QALY claims dominate the literature. Unfortunately, little attention is given as to how these claims might be evaluated for formulary decisions or whether formulary decision makers are actually interested in these claims

## Results

The main findings from the review of the 32 studies (Table 1) are:

- None of the studies presented their results in a evaluable form.
- None of the studies proposed a protocol or otherwise suggested how the claims might be evaluated.
- None of the studies addressed the issue of replication and the possibility of evaluating the claims for other target populations.
- 15 of the studies (47%) presented their results in a timeframe that excluded any possible evaluation: 28 years – 1 study; 30 years – 2 studies; 40 years – 3 studies; 50 years – 1 study; lifetime of subject cohort – 9 studies.
- None of the studies with results reported for timelines too long to support evaluable claims cautioned the reader that the claims were not evaluable and the possible implications of this for the credibility of the modeled results.
- One lifetime study (not included above) projected results over such a short survival span that evaluable claims were possible.
- 12 of the studies presented results in a period short enough (< 2 years) to support presenting evaluable claims.
- 3 of the studies presented results in a period (2 to 5 years) that could have been reformulated to generate claims for evaluation over a 2 year timeframe.
- QALYs were the primary endpoint in 19 studies.
- In the studies with a timeframe that excluded any possible evaluation all used cost-per-QALY as a primary endpoint.
- 30 of the 32 studies (94%) were supported by a pharmaceutical manufacturer
- In the 30 studies supported by a manufacturer, 29 (97%) reported results that supported the sponsor's product.

## Discussion

Three findings stand out from this systematic review:

- 15 of the 32 studies published in JME reported results in a timeframe that was clearly incapable of generating evaluable claims;
- None of the studies published in the JME proposed evaluable claims or how their claims might be evaluated; and
- An overwhelming proportion of studies in the JME (91%) were sponsored by manufacturers and supported the sponsor's product.

Even though 12 of the studies had the potential for evaluation, given the model time frame, it seems clear that the authors of these studies never intended the claims to be subject to empirical evaluation. The projections were to be taken at face value and, given the fact that virtually all were sponsored by a manufacturer, were intended (presumably) to influence formulary decisions.

From the decision-makers perspective, the claims put forward were driven by assumption. The models were extensively documented, data sources clearly referenced and limitations clearly set out. Emphasis was placed on the structure of the model, the application of relatively sophisticated techniques in decision modeling and state transitions, with appropriate account taken of uncertainty and likelihood claims for cost-effectiveness. What was missing was any attempt to translate the modeled claims to evaluable hypotheses and suggest protocols to support claims assessment, feedback to decision makers and replication.

The most egregious examples of modeled claims were the 15 studies that, in their choice of timeframe, were clearly incapable of generating evaluable hypotheses. Irrespective of whether or not decision makers were expected to take these claims seriously, the fact is that they met recommended standards for modeling. The IMS CORE Diabetes model and the Cardiff Diabetes model are well regarded and accepted model frameworks and were used in five studies<sup>22 23</sup>. The three studies using the IMS CORE diabetes model generated claims for both one-year and 30 years<sup>29 30 41</sup>. In the Gupta et al. study<sup>30</sup> the projections for India, Indonesia, and Saudi Arabia focused on life expectancy, cost, and complications related to diabetes and cost per QALY. While the analysis supported switching to the sponsor's product, the claims over 30 years were clearly not evaluable. The Home et al. study also used the IMS CORE Diabetes model and matched the Gupta et al. analysis in generating projections for 1-year and 30-year timeframes<sup>29</sup>. In this case, five countries were considered, including Mexico, South Korea, India, Indonesia, and Algeria, to assess the impact of starting insulin detemir in

insulin-naïve people with type 2 diabetes. The 30-year projections considered life expectancy, costs, complications, and cost-effectiveness. The 1-year model focused on treatment costs and quality of life. Initiating therapy with insulin detemir, the sponsor's product was found to be cost-effective in all countries. The Huetsen et al. lixisenatide type 2 diabetes analysis for Norway took a similar lifetime perspective, reporting on weight loss, lifetime healthcare costs, and QALYs. The modeled results supported the sponsor's product<sup>41</sup>. Two studies used the Cardiff diabetes model in Chinese populations<sup>47 52</sup>. The Gu et al. study for saxagliptin and the Deng et al. model for exenatide both reported results for a 40 year timeframe. While no funding was reported for the Deng et al. study, the Gu et al. study supported the sponsor's product.

The IMS CORE model and the Cardiff model simulations for time periods of 30 years and 40 years respectively are quite clearly not intended to generate comparative product claims that are evaluable, let alone replicable in target populations. There is not the remotest chance that the claims made over these timespans could ever be evaluated. The claims could, of course be taken at face value and as 'indicative' of implicit product superiority without any risk of contradiction, except for a possible competitive claim based on a competing long-term diabetes model. Such a clash of imaginary diabetic worlds is unlikely to resolve the debate. With what may seem an absurd timeframe, competing claims would still have no chance of ever being evaluated by an appeal to real world experimentation. Indeed, from a decision maker's perspective, any appeal to accept these 30 and 40 year claims at face value overlooks the fundamental point: we will never know whether they are right or even if they are wrong.

The same argument also applies to the other 10 published studies that have modeled claims over extended periods. These range from 28 years in the case of the Attard et al. study of pertuzumab, the Cure et al. study of sofosbuvir which followed a simulated cohort of 10,000 respondents until they reached 80 years of age, and the Meier et al. updated analysis of quadrivalent influenza vaccination (QIV) that, in one-year cycles, utilized a multi-cohort static Markov model that followed the youngest patient until they reached 100 years of age<sup>27 43 44</sup>.

Other long-term models were also potentially misleading. As one example, consider the flingolimod multiple sclerosis model for England<sup>32</sup>. The model utilizes a 50-year horizon lifetime cost-per QALY structure involving 21 health states. While the authors justify their choice of model as subscribing to the models used in NICE single appraisal submissions, the model is clearly not designed to generate evaluable hypotheses and the replication of study results. Even with the

NICE seal of approval (and the presumed acceptance by NICE that modeling imaginary worlds for 50-year time horizon is the technology assessment standard), the assumption-based claims are clearly nonsensical unless one is prepared to argue that they, sort of, reflect an expected future reality. A reality which is well outside any attempt at, say, GDP predictions or even demographic projections.

Against these examples of long-term or lifetime models, there are instances where a lifetime framework might make sense. Consider the yttrium-90 inoperable colorectal liver metastases model<sup>46</sup>. The survival profiles for those introduced to the therapy as well as those receiving best supporting care are so limited that a lifetime model may capture the relevant endpoints for a comparative assessment to be reported and replicated. Establishing evaluable claims is clearly possible given the modeled result that yttrium-90 is projected to result in a mean undiscounted life expectancy of 2.38 years compared to 1.03 years for best supportive care. There are also what may be described as intermediate models with claims expressed in a 2-year to a 5-year time frame. These include the Penn et al. 5-year model of cardiovascular biomarkers and the Thibault et al. 3-year model of memantine in Alzheimer's disease<sup>37 51</sup>. While these timeframes are probably not suited to effective reporting to formulary committees as part of ongoing disease area and therapeutic class reviews, there is a potential for these models to be reconsidered and claims expressed in a shorter and more evaluable timeframe.

Finally, there are models predicated on a  $\leq 2$ -year time frame. These clearly have the potential for evaluable claims, evaluation, and replication. They include the Evans et al. 12-month cost per QALY model of insulin degludec in the UK, the Lin et al. model of psychiatric relapse and recidivism in schizophrenia, through the 24 week Hofmacher and Borg et al. iron deficiency model, the O'Day 2-year model of relapsing-remitting multiple sclerosis in Sweden and the Toor et al. 1-year model of ulcerative colitis in Canada<sup>22 28 38 32 36</sup>.

Even so, without being unduly alarmist, the fact that 30 out of 32 studies were supported by manufacturers, and with 29 of these studies supporting the manufacturer's product must be a concern. The potential for bias in manufacturer sponsored modeled cost-effectiveness studies was recognized by the *New England Journal of Medicine (NEJM)* over 20 years ago<sup>24</sup>. As a result, manufacturer sponsored studies, or studies where there was a potential conflict of interest in authorship, were excluded from consideration and publication in *NEJM*. Even so, if there was no apparent conflict of interest, the *NEJM* was still prepared to publish modeled claims that did not meet the standards of normal science.

Unfortunately, attempts to assess possible bias in the choice of model and the specification of inputs are likely to be a fruitless exercise if the outcome is just another set of unevaluable claims. If there are concerns about bias and subscribing to the standards of normal science, there should be an appeal to the evidence. Competing claims can be evaluated through either retrospective or prospective observational evaluations, with the opportunity to replicate claims across a range of target populations.

#### *A Relativist Consensus?*

We might reasonably ask how, after some 30 years of promoting pharmacoeconomics and the modeling of competing claims, we have ended up sponsoring and publishing modeled claims that are either patently unevaluable, or potentially evaluable that are presented in a form that is unevaluable? One possibility is that consciously or not, pharmacoeconomics has put to one side application of the standards of normal science in favor of a relativist position that accepts modeled claims as a useful input to formulary decisions, irrespective of whether or not there is any empirical evidence to support the claims that are made. In other words, the adoption of an equivalence position that maintains that evidence is constructed within a particular social community. The process of discovering new facts is put to one side. If this argument is accepted, then what passes for a scientific research program in pharmacoeconomics, is a focus on rhetoric, persuasion and authority. The success of this program does not depend on its ability to generate new knowledge through the discovery of new facts and to reproduce or reject prior claims, but on its ability to mobilize the support of the community. To the relativist leaders of this community, normal science is not a way of coming to grips with reality.

#### *Truth is consensus.*

Whether or not one agrees that the thought leaders in pharmacoeconomics and the authors of many ISPOR standards subscribe to a relativist position, the fact remains that a substantial percentage of modeled claims for cost-effectiveness are accepted by journals such as the *JME*, *Value in Health* and *PharmacoEconomics* clearly fail the standards that are accepted in normal science. This position is compounded by agencies such as PHARMAC in New Zealand and Health Information and Quality Authority in Ireland in their adoption of the NICE reference case framework for manufacturer's submissions<sup>25 26</sup>. The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Academy of Managed Care Pharmacy (AMCP) with their *Format for Formulary Submissions* also encourage product claims built on simulations with no evaluable claims<sup>27 28</sup>. In contrast to pharmacoeconomics, in mainstream economics, there is an appreciation of the scientific method,

the formulation of hypotheses, the process of conjecture and refutation, and a commitment to the discovery of new facts. Even so, the issue of reproducibility is still of concern. In a recent paper, Camerer et al.<sup>29</sup> evaluated the replicability of microeconomic laboratory experiments. They found that in attempting to replicate 18 studies there was a significant (5%) effect in the same direction in only 61% of the studies and on average a replicated effect size of 66% of the original.

One possible reason for accepting a relativist position is that, at least outside of the US, the data environment is so limited that, unless considerable resources are expended, it is impossible to evaluate evaluable claims. The second best position (and least costly) is to accept modeled claims at face value, justifying our acceptance of those claims on the apparent sophistication of the model and our belief that it is a 'reasonable' reflection or representation of reality. This argument falls at the first hurdle. As Ellis and Silk point out in their critique of string theorists' claims that, the inherent elegance of a model should be sufficient for its acceptance without the need to evaluate evaluable claims<sup>30</sup>. Adopting this position avoids the critical question: what potential observational evidence would persuade us that the theory (or decision model) is wrong and lead us to abandoning it? If there is none, then it is not a scientific theory. As Wolfgang Pauli stated, in situations where an argument cannot be falsified by experiment, "This isn't right. This isn't even wrong"<sup>31</sup>.

#### *A Backlog of Unevaluable Claims*

Unfortunately, the accumulation of untested and unevaluable claims appears to be the hallmark of pharmacoeconomics. Few of the hundreds, if not thousands, of modeled projections published in the past 25 to 30 years have ever been exposed to evaluation, even though there has been ample time for modeled claims to be formulated empirically and evaluated. This observation applies equally well to modeled claims submitted to health technology assessment agencies. In the case of the PBAC in Australia, for example, where guidelines have been a requirement for formulary assessment for almost 25 years, there is no evidence to suggest that, for those modeled claims that have been submitted and accepted to justify product listing on the Pharmaceutical Benefits Scheme, that there have been any attempts to evaluate and replicate those claims in target patient populations. It has never been suggested that a protocol should accompany the modeled cost-effectiveness claim to facilitate evaluation in target treating population, let alone a commitment to the replication of claims.

For those who advocate non-evaluable simulated projections to support formulary decisions, their case is further weakened by the growing evidence (and concern) over the

lack of attempts to replicate empirical results and the inability to reproduce results in medicine, neuroscience, genetics and psychology. To the extent non-reproducible clinical results are factored into the assumptions supporting modeled claims for cost-effectiveness, the less credible are the claims based on those models. The fact that the claims are all too often non-evaluable merely adds to these concerns.

### Conclusions

The present review has focused on modeled cost-effectiveness claims. A similar evaluation could be directed at other subject areas, in particular burden of illness and cost of illness studies. While these rely, for the most part, on retrospective data, there are modeled claims for lifetime costs of illness which would likely fail the required standards. Even so, irrespective of whether the claim is defended on the grounds that it 'reflects reality', the standards for falsification and replication still apply. Authors and editors should recognize the importance, in judging the worth of modeled projections, that instead of taking them at face value, they should conform to the scientific method and support falsification and replication. Otherwise, we will face an ongoing accumulation of studies that lack credibility.

If the premise of this review is accepted, that claims for cost-effectiveness should meet the standards of normal science, then the editors of journals such as the *JME* need to consider whether it is possible to formulate an editorial policy that supports an ongoing process of developing and evaluating evaluable claims. A policy should recognize the importance of replication in establishing trust in scientific knowledge. This review has demonstrated that there are a number of instances where short-term modeled evaluations are capable of generating evaluable predictions. Journals such as the *JME* could take the next steps of encouraging authors to put claims in an evaluable form, to propose a protocol for claims assessment and, if possible, and report on the results of the claims evaluation.

**Table 1: Imaginary Worlds - Cost-Effectiveness Studies In The *Journal Of Medical Economics* January 2015 To December 2015**

Paper (author)	Target Population and Intervention	Sponsor (if any)	Modeling Technique and Claims Status	Claims Assessment and Credibility
Evans et al. <sup>32</sup>	Insulin degludec (IDeg) vs. insulin glargine (IGLAR) in a basal-bolus regimen for patients with type 1 diabetes in the UK	The study funded by Novo Nordisk the manufacturer of insulin degludec	Short-term (12 month) cost per QALY model. QALYs estimate by multiplying the number of hyperglycemic events by a time trade off estimate of the disutility per event. Outcomes: disutility values utilized for three mutually exclusive hypoglycemic events: non-severe daytime, non-severe nocturnal and severe). Results: IDeg cost effective vs. IGLAR with base case ICER £16,895/QALY with incremental QALY 0.0082	As a short term study there is a potential for replicating the study claims in a range of treating environments if the disutility framework and scores are applied. No evaluable claims presented and no protocol to detail how the short term results might be replicated. This might be considered important given incremental QALY claim over IGLar.
Henry et al. <sup>33</sup>	Renal denervation therapy (RDN) for resistant hypertension compared to standard of care in the Netherlands	The study was funded by Medtronic who manufacture the Symplicity RDN system	Markov lifetime state transition model with 34 health states and 7 clinical end points. Outcomes: lifetime cost-per-QALY. Results: RDN compared to standard of care cost-effective at conventional willingness to pay thresholds	With model results reported for a lifetime horizon there is no basis for evaluable claims.
Lafeuille et al. <sup>34</sup>	Canagliflozin and sitagliptin in type 2 diabetes patients with inadequate glycemic control	The study was funded by Janssen Scientific Affairs who market under license canagliflozin	Association between diabetes quality measures, blood pressure, low-density lipoprotein cholesterol and body weight, and health care costs. Economic simulation also undertaken to evaluate of changes in quality measures and incidence of adverse events associated with canagliflozin and sitagliptin on costs; Outcomes: regression analysis from insurance claims, EMRs and quality measure metrics to predict cost impacts. Results: simulation showed that changes in quality metrics and adverse event incidence observed in comparative Phase 3 DIA3015 trial comparing canagliflozin and sitagliptin resulted in PPPY healthcare cost reduction that favored canagliflozin	The authors pointed out that a modeled comparison based on the DIA3015 trial was most appropriate given the underutilization of canagliflozin in the market as approval only given in March 2013 compared to the earlier October 2006 approval of sitagliptin. A number of evaluable hypotheses and techniques are suggested by the analysis which could now be utilized to support a retrospective or observational evaluation of the simulated results.
Walter & Odin <sup>35</sup>	Continuous subcutaneous apomorphine (CSAI) in Parkinson's disease (PD) in UK and Germany	The study was funded by EVER Neuro Pharma the manufacturer of Dacepton (CSAI)	Markov lifetime state transition model with 12 health states with CSAI vs. standard of care, deep brain simulation (DBS) and levodopa/carbidopa intestinal gel (LCIG). Outcomes: costs, QALYs and	With model results reported for a lifetime horizon there is no basis for evaluable claims.



			life years (Lys). Results: CSAI a cost-effective therapy and a possible alternative treatment to LCIG or DBS in advanced PD	
Xuan et al. <sup>36</sup>	Bacterial lysates immunostimulant OM-85 in management of respiratory tract infections in China	The study was funded by Vifor Pharmaceuticals the manufacturer of OM-85	Acute treatment 6-month decision model comparing OM-85 with and without prophylaxis. Outcomes: costs and acute exacerbations or recurrent infections. Results: suggest it is a cost-effective intervention for both chronic bronchitis and rhinosinusitis	With a short time frame there is a potential for evaluating claims in both China and in French, Italian and Canadian settings where cost-effectiveness claimed
Attard et al. <sup>37</sup>	Neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory or early HER2-positive breast cancer in Canada	The study was funded by Hoffman-La Roche Ltd the manufacturer of pertuzumab (on acquiring Genentech)	Lifetime cost-per-QALY Markov state transition model with three health states (event-free, relapsed, dead) and a 1-month cycle for a 28-year time horizon. Two separate analyses utilizing total pCR data from NeoSphere and TRYPHAENA trials. Outcomes: achieving pCR response, event-free and overall survival and QALYs Results: the improvement in clinical efficacy and favorable cost-per-QALY against Canadian willingness to pay threshold showed pertuzumab to be an attractive treatment option	With model results reported for a 28-year time horizon there is no basis for evaluable claims.
Lin et al. <sup>38</sup>	Impact of psychiatric relapse and recidivism on adults with schizophrenia recently released from incarceration in Florida	The study was funded by Janssen Scientific Affairs	A 3-year Markov state transition model. Outcomes: psychiatric hospitalizations, infractions, arrests, re-incarcerations and direct costs of psychiatric hospitalization and costs to the criminal justice system. Results: Over 3 years, a relative 20% increase in proportion of patients receiving antipsychotic treatment substantially reduced total cumulative costs	With a short time frame there is the potential for evaluating claims. No evaluable claims were presented or a protocol to support claims assessment
Home et al. <sup>39</sup>	Starting insulin detemir in insulin-naïve subjects with type 2 diabetes in Mexico, South Korea, India, Indonesia and Algeria	The study was funded by Novo Nordisk the manufacturer of insulin detemir	Application of IMS Core Diabetes model over a 30-year timeframe to project impact of initiating insulin detemir. The assessment included also a 1-year analysis to capture QALYs. Outcomes: life expectancy clinical, costs and cost-effectiveness. Results: initiating insulin detemir increased life expectancy offsetting increased treatment costs, reduced diabetes related complications and claim for cost effectiveness in all 5 countries,	Projections over a 30-year time frame have no possibility of being evaluated and should be rejected; the 1-year projections have the potential to be evaluated in these countries (assuming data are available to support a prospective). No evaluable claims were proposed or a protocol to support claims evaluation in target populations
Gupta et al. <sup>40</sup>	Switching from biphasic human insulin 30,	The study was funded by Novo	Application of IMS Core Diabetes model over a 30-year timeframe to	Projections over a 30-year time frame have no

	insulin glargine, or neutral protamine Hagedorn to biphasic aspart 30 in type 2 diabetes (BAsp 30) in India, Indonesia and Saudi Arabia	Nordisk the manufacturer of BAsp 30	project impact of switching to BAsp 30. The assessment included also a 1-year analysis to capture QALYs. Outcomes: life expectancy ,clinical, costs and cost-effectiveness . Results: switching increased life expectancy, reduced diabetes related complications and was cost-effective or highly cost effective in all 3 countries over 30 years. The 1-year analysis showed switching to be cost-effective, but not as great as the effect over 30 years	possibility of being evaluated and should be rejected; the 1-year projections have the potential to be evaluated in these countries (assuming data are available to support a prospective). No evaluable claims were proposed or a protocol to support claims evaluation in target populations.
Huang et al. <sup>41</sup>	Linacotide vs. lubiprostone in adult patients with irritable bowel syndrome with constipation in the US	The study funded by Ironwood Pharmaceuticals and Forest Research Institute the manufacturers of linacotide (with rights acquired by Allergan in 2015)	Trial- based (12 week) decision model. Outcomes: number of responders, QALYs and total costs. Results: linacotide 290mcg QD less expensive, greater responsive and more QALYs gained than lubiprostone 8 mcg BID based on global assessment of symptom relief; for the IBS-QoL definition of response linacotide had lower costs and higher response rates for all but one one-way sensitivity scenarios.	With a 12-week timeframe (and the possibility of extrapolating from the clinical trial) there is potential for evaluable hypotheses to be evaluated. No evaluable claims were proposed or a protocol to support claims evaluation in target populations
O'Day et al. <sup>42</sup>	Natalizumab vs. fingolimod in relapsing remitting multiple sclerosis in Sweden	The study funded by Biogen Idec Inc the manufacturer of batalizumab	Two-year decision model. Outcomes: MS relapses avoided, cost per relapse avoided. Results: natalizumab dominates fingolimod	With a 2-year timeframe there is potential for evaluable hypotheses to be evaluated. No evaluable claims were proposed or a protocol to support claims evaluation in target populations
Sung et al. <sup>43</sup>	Posaconazole vs. fluconazole or itraconazole (FLU/ITRA) in prevention of invasive fungal diseases in US neutropenic patients	The study was funded by Merck the manufacturer of posaconazole	Update of trial based incremental cost-effectiveness model in 100 day trial plus follow-up framework. Outcomes: efficacy, IFD related mortality, death from other causes and direct medical costs. Results: posaconazole yielded fewer IFD events and lower overall costs	With a short time frame there is the potential for evaluating claims. No evaluable claims were presented or a protocol to support claims assessment
Nazir et al. <sup>44</sup>	Pharmacological treatments for overactive bladder focusing on mirabegron as first in-class selective $\beta_3$ -adrenoceptor agonist from a UK NHS perspective	The study was funded by Astellas Pharma Europe Ltd the manufacturers of mirabegron	Markov model with monthly cycle length and time horizon of up to 3 years to compare 2 different sequencies of up to 3 lines of oral therapy. Outcomes: (i) number of patients with controlled symptoms (no incontinence episodes and <8 micturitions per 24 h); (ii) patients with no incontinence episodes per 24	With a 1-year timeframe there is potential for evaluable hypotheses to be evaluated. No evaluable claims were proposed or a protocol to support claims evaluation in target populations

			hours; and (iii) patients with <8 micturitions per 24 h. Results: new treatment sequence of including recently approved agent as 3 <sup>rd</sup> line before considering other treatment options over a 1-year time horizon associated with greater number of controlled patients and fewer incontinence episodes but higher costs compared to standard treatment sequence.	
Zachariah & Samnaliev <sup>45</sup>	Echo-based screening of rheumatic heart disease in children	The study funded by National Heart, Lung, and Blood Institute Career Development Award	Population-based Markov 2-stage screening model comparing screening to no screening running over 40 years. A yearly time cycle comparing societal costs and QALYs between current practice of routine clinical exam detection and population based rapid echocardiography rsingle screening followed by full echo in screen positive opatients. Outcomes: costs, QALYs and ICER per QALY. Results: 2-stage screening and secondary prophylaxis may achieve modestly improved outcomes at a lower costs	Projections over a 40-year time frame have no possibility of being evaluated and should be rejected. . No evaluable claims were proposed or a protocol to support claims evaluation in target populations
Toor et al. <sup>46</sup>	Infliximab, adalimumab, and golimumab in moderately to severely active ulcerative colitis	The study was funded by Janssen Inc Canada the manufacturers of golimumab	One-year Markov model with 8-week induction period and 22 subsequent 2-week cycles up to 1-year for three tumor necrosis factor inhibitors (infliximab, adalimumab, and golimumab) in comparison to conventional therapy.. Outcomes: short-term costs per sustained remission and sustained response. Results: Lowest costs of one full year remission and response for golimumab 100mg followed by golimumab 50mg	With a one year time frame potential for evaluating claims. No evaluable claims were presented or a protocol to support claims assessment in target populations
Penn et al. <sup>47</sup>	Impact of implementing a multiple inflammatory biomarker –based approach to identify, treat and reduce cardiovascular risk	The study supported by Cleveland Heart Lab Inc. a manufacturer of cardiovascular biomarkers	Modeling of change in number of events and costs after routine implementation of routine risk-stratification with multiple inflammatory biomarker approach. Outcomes: estimated events for a one million member health plan over 5-years (fatal MI and IS events( and cost savings. Results: substantial prospective events avoided and cost savings over 5-years	With a shorter time frame than 5 years, there is the potential for evaluating claims. No evaluable claims were presented or a protocol to support claims assessment in target populations.
Hofmarcher & Borg <sup>48</sup>	Ferric carboxymaltose in iron deficient patients with chronic	The study was supported by Vifor Pharma Nordiska	Twenty-four week cost per QALY model (vs. placebo). Outcomes: direct medical costs and QALYs. Results: ICER	With a short time frame there is the potential for evaluating claims. No

	heart failure in Sweden	AB the manufacturers of ferric carboxymaltoser	at €8,194/QALY below notional Swedish WTP threshold of €53,300/QALY.	evaluable claims were presented or a protocol to support claims assessment
Kuwabara et al. <sup>49</sup>	Simeprevir with peginterferon (PR) and ribavirin vs. telaprevir with ribavirin, PR alone or no treatment in treatment-naïve chronic hepatitis C genotype 1 patients in Japan	The study was supported by Janssen Pharmaceutica NV the manufacturer of simeprevir	Markov model to map the progression of HCV to estimate average life years and lifetime average costs. Outcomes: ICERs and incremental costs and life years. Results: SMV with PR compared to telaprevir with PR and PR alone was dominant with life years gained at a lower cost	With model results reported for subject lifetimes there is no basis for evaluable claims.
Laires et al. <sup>50</sup>	Adding ezetimibe to atorvastatin vs. switching to rosuvastatin therapy for high cardiovascular risk patients in Portugal	The study was supported by Merck Sharp & Dohme the manufacturer of the combination product ezetimibe/atorvastatin	Lifetime cost-per-QALY Markov model with annual cycles (up to age 100 years). Outcomes: lifetime costs and life years/QALYs. Results: base case ICER estimated at €16,465. As this is below Portuguese WTP threshold of €30,000/QALY adding ezetimibe vs. switching to rosuvastatin is cost-effective	With model results reported for subject lifetimes there is no basis for evaluable claims.
Huetson et al. <sup>51</sup>	Once-daily GLP-1 receptor agonist lixisenatide vs. bolus insulin both in combination with basal insulin for type 2 diabetes in Norway	The study was supported by Sanofi the manufacturer of lixisenatide	Application of IMS Core Diabetes model to project lifetime cost-per-QALY. Subjects assumed to receive combination treatment with basal insulin, lixisenatide or bolus insulin for 3 years followed by intensification of basal-bolus insulin for their remaining lifetime. Outcomes: weight loss, lifetime healthcare costs and QALYs. Results: lixisenatide reduced lifetime healthcare costs and increased QALYs. ICER below Norwegian willingness to pay threshold.	With model results reported for subject lifetimes there is no basis for evaluable claims.
Muser et al. <sup>52</sup>	Paliperidone palmitate vs. oral antipsychotics in schizophrenia	The study was supported by Janssen Scientific Affairs the manufacturer of paliperidone palmitate	Trial-based cost-outcomes model (15 months) PRIDE. Objectives: to assess comparative ICER for costs (not collected in trial) incurred to first treatment failure (healthcare or criminal justice system) comparing paliperidone palmitate with antipsychotics. Results: ICERs favored paliperidone palmitate ranging from \$17,391 per psychiatric hospitalization (HC) or criminal justice system (CJS) event avoided to \$77,731 per patient that avoided any incarceration compared to oral antipsychotic group. Costs for HC or CJS events avoided offset 25% of the greater drug cost with paliperidone palmitate.	The relatively short time frame (and the ability to modify timeframe) there is a potential for generating evaluable claims for a range of post-incarceration settings and CJS costs. No evaluable claims were provided..

Cure et al. <sup>53</sup>	Sofosbuvir plus ribavirin with or without pegylated interferon for chronic hepatitis C in Italy	The study was supported by Gilead Sciences the manufacturer of sofosbuvir	Markov cost-per-QALY model with subjects followed (cohort of 10,000) until reached 80 years of age. Based on models published by Southampton Health Technology Assessment Centre for NICE. Outcomes: overall for the for the 6 HIV genotype groups analyzed the SOF-based regimens gave a favorable cost-effectiveness profile versus standard of care	With model results reported for subject lifetimes there is no basis for evaluable claims.
Meier et al. <sup>54</sup>	Updated analysis of quadrivalent influenza vaccination versus trivalent influenza vaccination in at-risk adults and the elderly in the UK	The study supported by GlaxoSmithKline Biologicals the manufacturer of QIV	Update of a lifetime, multi-cohort static Markov model run in 1-year cycles until youngest patients at entry achieved age of 100 years. Outcomes: influenza cases avoided, hospitalizations and deaths avoided , costs and QALYs compared to TIV. Results: QIV was estimated to be cost-effective in 68% of simulation with a cost-per-QALY threshold of <£20,000.	With model results reported for subject lifetimes (simulated to age 100 years) there is no basis for evaluable claims.
Peng et al. <sup>55</sup>	DTG+ABC/3T versus EFV/TDF/FTC for first line treatment of HIV-1 in the US	The study was supported by Bristol-Myers Squibb who acquired DTG from GlaxoSmithKline	Lifetime discrete event simulation model for lifetime CD4 counts, clinical events, treatment switching and death. Outcomes: lifetime discounted medical costs, QALYs and ICERs. Results: DTG+ABC/3TC resulted in higher costs and only slightly increased QALYs with an ICER that exceeded standard cost-effectiveness threshold. Incremental benefits may not be worth incremental costs.	With model results reported for subject lifetimes there is no basis for evaluable claims.
Pennington et al. <sup>56</sup>	Selective internal radiation therapy using yttrium -90 resin microspheres in inoperable colorectal liver metastases versus best supporting care in the UK	The study was supported by Sirtex Medical Ltd the manufacturer of yttrium -90 resin microspheres	State-transition, trial based lifetime cost-per-QALY model with a daily cycle. Outcomes: QALYs per life year gained, discounted costs and adverse events. Results: compared to best supportive care SIRT using yttrium -90 resin microspheres is a clinically effective and cost-effective option	Given the anticipated life expectancy of target patients there is the potential to develop evaluable hypotheses to evaluate outcomes in UK and other treatment settings. No evaluable claims or a protocol for possible evaluations were proposed.
Gu et al. <sup>57</sup>	Saxagliptin vs. glimepride as second line addred to metformin in type 2 diabetes in China	The study was supported by AstraZeneca who (in collaboration with Bristol-Myers Squibb) is the manufacturer of saxagliptin	Application of Cardiff diabetes model to simulate disease progression and long-term impacts over a 40-year period. Outcomes: mcosts, events incidence and QALYs. Results: Saxagliptin + metformin more cost-effective with fewer adverse effects	With results reported for a 40-year timeframe there are no evaluable claims.
Rajagopalan et al. <sup>58</sup>	Lurasidone vs. quetiapine XR in bipolar	The study was supported by	Three-month trial-based cost-effectiveness model. Outcomes	With a 3-month time frame, there is the

	depression	Sunovion Pharmaceuticals the manufacturer of lurasidone	measure percentage of patients achieving remission (MADRAS total score $\leq 12$ by weeks 6-8). Outcomes: a greater percentage of lurasidone XR patients achieved remission, with lurasidone having a 86% probability of being cost-effective. .	potential for evaluable claims to evaluate cost-effectiveness in bipolar depression and to report results to decision makers. No evaluable claims were proposed although author's pointed to the possibility of product impact assessments over longer periods and in real world settings.
Westerhout et al. <sup>59</sup>	Simeprevir used with. peginterferon + ribavirin in management of genotype 1 hepatitis C in the UK	The study was supported by Jansen EMEA the manufacturer of simeprevir	A 2-phase cost-utility model with therapy efficacy captured in first phase and a second Markov phase of long-term post-treatment to capture lifetime outcomes. Health state utilities were the principal outcome. Results: SMV+PR a superior treatment option	With results reported for a 40-year timeframe there are no evaluable claims.
Maruszczak et al. <sup>60</sup>	Flingolimid vs. dimethyl fumarate in highly active relapsing-remitting multiple sclerosis in England	The study was supported by Novartis Pharmaceuticals the manufacturer of flingolimid	Lifetime cost-per-QALY cohort Markov model to determine cost-utility of oral DMTs in HA RRMS, to include conversion to secondary progressive MS (SPMS) involving 21 states. The Markov structure was based on models used in all NICE single technology appraisal submissions for DMTs in RRMA. Outcomes: QALYs and costs over a lifetime horizon modeled as 50 years. Results: flingolimid is cost-effective in HA RRMS following the introduction of DMT to the UK market.,	With results reported for a 50-year timeframe there are no evaluable claims.
Thibault et al. <sup>61</sup>	Memantine ER + cholinesterase inhibitor monotherapy vs. memantine ER as monotherapy in moderate-to-severe Alzheimer's [sic] type in the US	The study was supported by Forest Research Group (affiliate of Actavis). Actavis is the manufacturer of memantine ER	A 3 year cost-per-QALY evaluation using a modified version of the AHEAD II discrete event simulation model. Outcomes included (i) clinical impairment, (ii) health related QoL, mean time in institution, mean time with SIB severity, mean time without severe and mean time on antipsychotics, and (iii) direct medical costs and caregiver costs. Results: over 3-years memantine ER combined with cholinesterase inhibitors gave better clinical outcomes and lower costs, with a favorable ICER per QALY gained.	As a short term study there is potential, as the authors indicate, for prospective observational studies to generate more accurate projections of disease progression and treatment effectiveness. No evaluable propositions were presented. To support claims for clinical and cost-effectiveness..
Deng et al. <sup>62</sup>	Cost-effectiveness of exenatide vs. insulin glargine in Chinese type	No funding sources reported	Application of Cardiff diabetes model with a 40-year timeframe. Outputs: macrovascular and microvascular	With results reported for a 40-year timeframe there are no evaluable claims.

	2 diabetes patients inadequately controlled by oral therapies		complications, diabetes-specific mortality, costs and QALYs Results: exenatide as an add-on therapy is cost-effective compared to insulin glargine.	
Muduma et al. <sup>63</sup>	Budget impact comparison of Advagraf versus Prograf in renal transplantation as primary immunosuppressive medication	The study was supported by Astellas Pharma EMEA Ltd the manufacturer of Advagraf	Five-year budget impact cost-adherence model structured as a decision tree followed by a 4-state Markov model with monthly cycle length. Outcomes: costs, antibody-mediated rejection and graft Results: over five years a cost saving with Advagraf from a UK perspective in renal transplant recipients]	As a short term budget impact model, there is the potential for developing empirically assessable claims in a time frame of less than 5 years. No evaluable claims or a protocol for evaluating claims were presented.

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