Title: Economic evaluations of pharmaceuticals without randondomised controlled trials: a systematic review and taxonomy

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Abstract (247 / 250)

Background

Pharmaceuticals are usually granted a marketing authorisation on the basis of randomised controlled trials (RCTs). Occasionally the efficacy of a treatment is assessed without a randomised comparator group (either active or placebo).

Objective

To identify and develop a taxonomic account of economic modelling approaches for pharmaceuticals licensed without randomised control trial data.

Methods

We searched PubMed, the websites of UK health technology assessment (HTA) bodies and the ISPOR Scientific Presentations Database for assessments of the 74 indications granted a marketing authorisation by the FDA or EMA from Jan-1999 to May-2014 without RCT data. The outcome of interest was the approach to modelling efficacy data.

Results

Fifty-one unique models were identified based on 29 peer-reviewed articles, 30 health technology appraisals (HTAs), and 15 ISPOR abstracts concerning 30 indications (44 indications had not been modelled). Also notable was the low rate of submission to HTA agencies (28/98).The majority of models (43/51) were based on 'historical controls' – comparisons to previous meta-analysis or pooling of trials (5), individual trials (19), registries/case series (14), or expert opinion (7). Other approaches used the patient as their own control, performed threshold analysis, assumed time on treatment was added to overall survival, or performed cost-minimization.

Conclusions

There is considerable variation in the quality and approach of models constructed for drugs granted a marketing authorisation without a RCT. The most common approach is of a naïve comparisons to historical data (using other trials / registry data as a control group), with considerable scope for bias.

Key points for decision makers

- When pharmaceuticals are licensed without comparative data, economic models are generally constructed using a historical control
- Even within evaluations using the same method, the quality and appropriateness of an approach varies
- The appropriateness of historical comparison for modelling using uncontrolled study data requires further methodological evaluation

Article: Word count: 2261

1. Introduction

Treatments are usually granted a marketing authorisation on the basis of randomised controlled trials, conducted against either a placebo or an active control[1]. This provides a good basis for regulators to make decisions regarding the efficacy of interventions compared to the current standard of care [2]. This evidence may then be used to estimate the difference between the new treatment and the standard of care. Indirect treatment comparisons using a common comparator sometimes enable the comparison of the efficacy of treatments in different studies[3,4].

Less commonly, treatments can be granted a marketing authorisation without a study containing a control arm. In a few cases it may be 'obvious' that the treatment is efficacious, for example if all patients died before an intervention was available, but all live afterwards[5], or patients achieve a marked improvement in an objective measure, for example blood count[2]. Whilst these treatments may receive a license for their use, estimates of their comparative efficacy compared to the currently used treatment are still needed to inform decisions on reimbursement in many healthcare systems. This may be to show the clinical improvement for patients, or alternatively for cost-effectiveness analysis, used in many countries for resource allocation decisions[3].

Where cost-effectiveness analysis is used as a criterion in healthcare systems, treatments are required to generate more health (usually defined in terms of quality adjusted life years) than the treatments that would be displaced (represented by a 'shadow budget'), i.e. that the money spent on the new intervention would not be better spent elsewhere. How such estimates should be constructed without controlled trials is however unclear – whilst there exists extensive guidance on constructing economic models based on RCT results, there is no guidance on the most appropriate method of modelling uncontrolled study data from health technology agencies or professional bodies (Table 1).

The objective of this study was therefore to identify models constructed for treatments granted marketing authorisation without controlled clinical trial evidence, and the approach taken to estimating relative efficacy between the treatment(s). Of relevance to the study were both published economic models and health technology appraisals.

2. Methods

Hatswell et al. [6] identified 74 indications granted a marketing authorisation by either the FDA or the EMA from 1999 to May 2014, on the basis of uncontrolled clinical trial results. We conducted a systematic review for economic evaluations published for each of the treatments listed using PubMed (search terms given in Figure 1). Searches were also conducted for health technology appraisals conducted by the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and All Wales Medicines Strategy Group (AWMSG), as well as the grey literature of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Scientific Presentations Database.

After identification, results (papers, health technology appraisal submissions and scientific presentations) were filtered for models constructed in the relevant indications with uncontrolled

study data (some treatments had multiple indications, which was what the publication investigated, or subsequently had RCTs conducted). Results were then de-duplicated based on the model descriptions and study authors, to account for the same model being used for different purposes (for example a model used in a NICE submission, then published with Spanish costs, all whilst using the same approach to modelling efficacy). Where it was not clear whether a model was reported on multiple occasions, or was a similar approach, this was discussed by the reviewers and a decision reached by consensus.

Following identification of the economic models, the approaches used to estimate efficacy against the relevant comparator were categorised for each model. If a model included multiple approaches to modelling efficacy data, these were classed as separate approaches. The resulting models were then placed in to a taxonomic framework and analysed for commonality in approach.

3. Results

Figure 2 shows the PRISMA diagram for economic evaluations retrieved through PubMed [7]. The initial 74 searches yielded 1202 hits, which were reduced to 56 full articles after abstract and title review. Twenty nine papers were included in the final analysis. The main reasons for exclusion on full paper review were models being based on RCT data (n=9), considering a different indication (including a different stage of the same disease, n=7) and papers that did not contain an economic model (e.g. burden of illness studies, n=6).

In addition to published papers searches of health technology body websites led to 19 NICE appraisals being identified (9 included), 52 SMC appraisals identified (16 included), and 27 AWMSG appraisals identified (5 included). Overall there was a notable level of non-submission to HTA agencies, in particular to the SMC (13/52 non-submissions) and AWMSG (13/27 non-submissions). Appraisals also often occurred after RCT based results had become available (NICE 8/19, SMC 9/52, AWMSG 3/27) leading to exclusion from this study. Full results of the review are shown in Table 1.

Searching the ISPOR Scientific Presentations Database led to 1780 abstract hits, with 43 records selected for further review and 29 full records included. The most common reason for exclusion was insufficient information reported regarding the model or approach used (n=14).

In total, 74 relevant documents were identified (including publications, health technology appraisals and scientific presentations), which described 91 distinct modelling approaches. After consolidation of approaches reported multiple times (for example one model being used for NICE and SMC submissions, presented at ISPOR and then published in an indexed journal), 51 unique approaches were identified. Of these 51 models, the overwhelming majority (n=43, 84%) were based on historical controls. Other approaches identified included using patients as their own control either through statistical analysis or comparisons with baseline values (n=3, 6%), cost minimisation analyses (n=3, 6%), threshold analyses (n=1, 2%), or assuming in oncology that time in progression free survival was added to overall survival, with treatments then given in sequence (termed the 'cumulative method'; n=1, 2%) (Figure 3).

All the 43 historical controls identified compared the results of the uncontrolled study of the new treatment to a separate set of data. In 17 cases (40%) the new treatment was compared to one arm

from another clinical study and in 5 cases (12%) pooled or meta-analysed data from a series of studies. A further 14 models (33%) used comparisons to registry or case series data, with 7 models (16%) comparing the results of the uncontrolled study to expert opinion. Trial and registry data appeared to be used interchangeably in evaluations, with only seven studies (16%) attempting to account for differences in patient characteristics or patient selection.

4. Discussion

The results of this review show that 51 unique models have been published for 30 different indications granted a marketing authorisation without a comparative trial. Consequently of the 74 indications approved without a comparative trial, [6] 44 indications have therefore not been modelled and estimates of cost-effectiveness are available. It is not known what the rate of economic evaluation of new indications is, although we suspect it will be higher than the 40% rate seen in this study.

The use of historical control was by far the most common approach (43/51), which was most frequently taken from another trial or trials (22 of the 43). However, even within this method there was substantial variation – some studies compared the results of uncontrolled trials to results taken from multiple trials (for example Dinnes et al. who pooled the results of 8 other clinical trials to compare against), whereas the majority of models compared against single arms from other studies.

The assumption inherent in naïve comparisons to historical controls (first proposed by Pocock[8]) is that patients are similar, or "exchangeable", between studies. If this is not the case, and patient systematically differ, then this procedure will introduce bias in the results. Several approaches to matching patients and baseline characteristics between studies are available in the literature, including methods based on propensity scores,[9] and match adjusted indirect comparisons [10]. Despite the availability of these approaches, only 2 models attempted to control for any differences between trials, with one notable outlier being the work by Annemans et al. [11], who constructed a historical control by reviewing patient records at the centres that participated in the clinical trial, in the time period before the clinical trial was open for enrolment [11].

The lack of adjustment of outcomes to reflect potentially more favourable patient cohorts may represent a substantial bias in the literature in favour of the new treatments. A study by Sacks, Chalmers & Smith of 50 RCTs and 56 historically controlled trials of the same interventions, the randomised control arm performed better than the historical control arm. In the studies cited therefore 79% of historically controlled trials stated the intervention was effective, compared to only 20% of RCTs[12]. Diehl & Perry investigated the same question looking at overall survival or relapse free survival in oncology, finding 43 examples in the literature of well-matched historical cohorts and RCT control groups. However when comparing the outcomes of the two groups, 18 of the 43 studies had a greater than 10% difference in effect size between the control groups – the randomised group performing better on 17/18 occasions [13]. This latter finding is particularly concerning given 32 of the 43 historically controlled models were in oncology, though other examples historical controls have proved a poor match for RCT control arms that would be expected to have shown similar results. [14–16]

Outside of historical controls, cost minimisation (though frowned upon in the literature[17]) was used in 3 models – whilst it may appear superficially attractive to assume treatments have equal efficacy to similar ones, it is unlikely that they exhibit exactly the same efficacy, with zero uncertainty. A further 3 models compared patient outcomes on treatment to a patient's baseline result. This is also a potentially biased approach, due to issues such as regression to the mean[18]. One additional approach, comparing all patients to non-responders, allows the estimation of an effect size; however it will be overly favourable towards the intervention, as non-responders will include an inherently sicker population [19]. The final approach noted was that of Tappenden et al., who pragmatically performed threshold analysis of the relative risk needed for the drug to be considered cost-effective. Although this does not necessarily give an estimate of effect size, it allows a decision maker to make a more informed decision after reviewing the clinical evidence[20], as such we would recommend the use of similar threshold analyses where appropriate.

That there is a number of differing approaches to modelling, with a lack of standard approach to handling issues such as patient selection, is likely a reflection of the relative rarity of evaluations with this type of data (we identified only 51 models, compared to the vast literature of health economic evalatons published[21]). Despite the lack of standard approaches and guidelines however, some studies appear to be well conducted, with attempts to select an approach based on reasonable assumptions, and control for any patient selection (for example Woods et al.[22]).

5. **Conclusion**

The majority of treatments granted a marketing authorisation without controlled study results have not been subject to economic evaluation in a published form, with also a high level of non-submission to UK health technology agencies for such products. The evaluations that have been performed were generally based on naïve comparisons to historical controls from individual arms of clinical trials, or registry/case series data.

Further research and guidance is required on the appropriateness of historical controls in economic evaluation, and on the most relevant methods to use when modelling uncontrolled data with the aim of estimating comparative effectiveness. Ultimately formal guidance and standardisation may reduce the level of bias in economic evaluations, and lead to an improvement in the average quality of published models. Standardisation would also provide a basis for comparison between studies, such that interventions can be more readily compared with other approaches to evaluation, where methods are comparable [23].

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Tables & Figures

Table 1: Tabulated PRISMA diagram of the number and source of economic evaluations identified as being based on uncontrolled clinical study data

	NICE	SMC	AWMSG	ISPOR	PubMed	Totals
Number of hits	19	52	27	1793	1235	**3182**
Non-submissions	2	13	13	-	-	**28**
For review	17	39	14	43	56	**142**
Excluded	8	23	9	28	27	**95**
Different indication	0	0	1	2	7	**11**
Different drug or intervention	0	0	0	4	3	**7**
Clinical paper or commentary	0	0	0	1	1	**2**
Not an economic model	0	5	0	2	6	**13**
Model based on RCT data	8	9	3	5	9	**33**
Insufficient information	0	9	5	14	1	**29**
Included	**9**	**16**	**5**	**15**	**29**	**74**

Table 2: Economic models identified as having been based on uncontrolled clinical study data

Drug	Disease area	Approach taken	Historical control?	Source of historical data	Data adjusted?	Year	Reference
Anagrelide	Essential thrombocytopenia	Decision tree comparing outcomes with treatment to patient baseline	No	-	-	1999	[24]
Anagrelide	Essential thrombocytopenia	Markov model using other expert opinion on the efficacy of treatments	Yes	Expert opinion	-	2002	[25]
Anagrelide	Essential thrombocytopenia	Markov model using historical control data from a trial for the main comparator and no treatment	Yes	Trial	-	2005	[26]
Argatroban	Heparin-induced thrombocytopenia	Trial data used for the drug, with historical data from the same hospitals involved in the trial used for the comparator	Yes	Case series	-	2006	[27]
Argatroban	Heparin-induced thrombocytopenia	Trial data used for the drug, with case series data used for the control	Yes	Case series	-	2007	[28]
Argatroban	Heparin-induced thrombocytopenia	Decision tree model using historical control data from hospitals for both treatment and control	Yes	Case series	-	2012	[29,30]
Argatroban	Heparin-induced thrombocytopenia	Decision tree model using an assumption of equal efficacy (cost minimisation)	-		-	2013	[31]
Busulfan	Haematopoietic progenitor cell transplantation	Decision tree model using unadjusted trial results to compare the treatment and comparator	Yes	Trial	-	2012	[32]
Temozolomide	Anaplastic astrocytoma	Compares trial results to a meta-analysis of trials of the comparator treatment	Yes	Meta-analysis	-	2000	[33]
Temporfin	Head and neck cancer	Trial results for the treatment compared naively to the control arm of a clinical trial for another treatment	Yes	Trial	-	2004, 2005	[34,35]
Gemtuzumab Ozogamicin	Acute myeloid leukaemia	Trial data for the drug compared with hospital data for the comparator. The group were matched for demographics	Yes	Case series	Yes	2002	[36]
Alemtuzumab	Chronic lymphocytic leukaemia	Assumption made of identical efficacy between products, with naïve comparison of trials used as sensitivity analysis	-	-	-	2007	[37]
Imatinib Mesylate	Chronic myeloid leukaemia	Single arm study used for treatment results, which are compared (unadjusted) to the results of the comparator taken from an RCT	Yes	Trial	-	2002-2004	[38–40]
Imatinib Mesylate	Chronic myeloid leukaemia	Single arm study used for treatment results, which are compared to expert opinion for the comparator	Yes	Expert opinion	-	2002-2003	[38,40,41]
Imatinib Mesylate	Gastrointestinal stromal tumours	Exponential curve fitted to the trial data for imatinib, naively compared to a historical control from a trial	Yes	Trial	-	2003 - 2007	[42–44]

Drug	Disease	Description				Year	Reference
Imatinib Mesylate	Gastrointestinal stromal tumours	Trial data for imatinib compared to a case series for the comparator	Yes	Case series	-	2003	[45]
Cetuximab	Colorectal cancer	Trial data used for cetuximab, with the comparator effectiveness estimated by reducing the survival based on results from another trial	-	-	Yes	2007	[46,47]
Cetuximab	Colorectal cancer	Trial data used for cetuximab, using a naïve comparison to results from another trial which included the comparator	Yes	Trial	-	2007	[20,48]
Cetuximab	Colorectal cancer	Trial data used for cetuximab, with threshold analysis performed how ineffective the comparator would need to make cetuximab cost-effective	-	-	-	2007	[20,48]
Cetuximab	Colorectal cancer	Trial data used for cetuximab, with case series data taken from the same hospitals used as the control arm	Yes	Case series	-	2007	[11]
Trabectedin	Soft tissue sarcoma	Uncontrolled trial data compared naively to pooled data from two trials for the comparator (ifosfamide)	Yes	Pooled trial data	-	2008-2011	[49–52]
Trabectedin	Soft tissue sarcoma	Uncontrolled trial data for trabectedin compared with pooled data from four trials for the comparator, with adjustments made to account for differences in baseline characteristics	Yes	Pooled trial data	Yes	2009-2013	[53–57]
Trabectedin	Soft tissue sarcoma	Progression free survival taken from studies of the comparators then compared naively. All patients then assumed to have equal post progression survival	Yes	Pooled trial data	-	2014	[58,59]
Cladribine	Hairy cell leukaemia	Naïve historical control of results pooled trial data clinical trials. Results from the studies were adjusted for patient disease status, but not demographic characteristics	Yes	Pooled trial data	Yes	2007	[60]
Gefitinib	Non-small cell lung cancer	Naïve comparison of gefitinib uncontrolled clinical study to the best supportive care arm from a RCT in the same disease area	Yes	Trial	-	2004	[61]
Clofarabine	Acute lymphoblastic leukaemia	Compared outcomes from the drug to results from a registry matched to patient characteristics	Yes	Registry	Yes	2006, 2007	[62,63]
Nelarabine	T-cell acute lymphoblastic leukaemia / lymphoma	Trial data for Nelarabine compared to historical trial data for the comparator	Yes	Trial	-	2008, 2009	[64,65]
Betaine Anhydrous	Homocystinuria	Decision tree comparing results of an uncontrolled study to results seen in a registry	Yes	Registry	-	2010	[66]
Alglucosidase Alfa	Pompe disease	Uncontrolled data compared to matched registry data	Yes	Registry	Yes	2007, 2012	[67,68]
Alglucosidase Alfa	Pompe disease	Trial data compared naively to registry data from the disease area	Yes	Registry	-	2014	[69]

Sunitinib Malate	Renal cell carcinoma	Uncontrolled trial data compared to a published case series and a Medicare case series	Yes	Case series	-	2007, 2009	[70–73]
Sunitinib Malate	Renal cell carcinoma	Expert opinion used to estimate the benefit of sunitinib	Yes	Expert opinion	-	2007	[74]
Sunitinib Malate	Renal cell carcinoma	Trial data for sunitinib compared to a Finnish case series	Yes	Case series	-	2007, 2008	[75,76]
Dasatinib	Chronic myeloid leukaemia	Uncontrolled study data for dasatinib compared to trial data for the comparator	Yes	Trial	-	2007, 2009	[77–79]
Dasatinib	Chronic myeloid leukaemia	Uncontrolled study data for dasatinib compared to trial data for the comparator	Yes	Trial	-	2007, 2009	[77–80]
Dasatinib	Philadelphia chromosome-positive acute lymphoblastic leukaemia	Historical control for the comparator compared to trial data for dasatinib	Yes	Trial	-	2007	[80]
Bortezomib	Mantle cell lymphoma	Trial data compared to historical control taken from a Canadian cancer registry	Yes	Registry	-	2009	[81]
Nilotinib Hydrochloride Monohydrate	Chronic myeloid leukaemia	Results from clinical trials for each of the comparators used in the model without adjustment	Yes	Trial	-	2008, 2009	[78,82]
Nilotinib Hydrochloride Monohydrate	Chronic myeloid leukaemia	Uncontrolled study results for each of the comparators	Yes	Trial	-	2011	[83]
Nilotinib Hydrochloride Monohydrate	Chronic myeloid leukaemia	Response rates taken from clinical studies for each of the comparators, then used to predict survival based on this surrogate outcome	Yes	Trial	-	2009	[84]
Tocofersolan	Vitamin E deficiency due to cholestasis	Trial results for the treatment, with expert opinion used for the comparator	Yes	Expert opinion	-	2012	[85]
Ofatumumab	Chronic lymphocytic leukaemia	Non-responders assumed to represent the outcome for untreated patients	-	-	-	2010-2013	[19,86–89]
Carglumic acid	Chronic hyperammonemia	Comparator data taken from an Italian hospital	Yes	Case series	-	2013	[90]
Asparaginase Erwinia Chrysanthemi	Acute lymphoblastic leukaemia	Assumption made of equal efficacy for all treatments (cost-minimisation)	-	-	-	1995	[91]
Brentuximab Vedotin	Hodgkin's lymphoma	Trial data used for the drug, with a systematic review conducted for comparator data, which was then adjusted for differences in patient characteristics between trials	Yes	Trial	Yes	2012	[22]
Defibrotide	Veno-occlusive disease	Trial data used for defibrotide, with then selected patients from a case series used for comparator data	Yes	Historical control	Yes	2014	[92]

Bosutinib	Chronic myeloid leukaemia	Surrogate outcome of response rate taken from each comparator and used to estimate outcomes	Yes	Trial	-	2013	[93–95]
Bosutinib	Chronic myeloid leukaemia	Time on treatment for each drug assumed to be additive to estimate overall survival	-	-	-	2013	[93,96]
Bosutinib	Chronic myeloid leukaemia	Trial data for the drug compared to expert opinion of survival for untreated patients	Yes	Expert opinion	-	2013	[95]
Bosutinib	Chronic myeloid leukaemia	Trial data for the drug compared to expert opinion of survival for untreated patients	Yes	Expert opinion	-	2013	[95]

Figure 1: PubMed search terms for cost-effectiveness papers

1. *Generic drug name*
2. *Drug brand name EU*
3. *Drug brand name US*
4. Or 1-3

5. Cost-Benefit Analysis
6. Cost-utility
7. Cost-effectiveness
8. Pharmacoeconomic*
9. health economic*
10. cea
11. cua
12. markov*
13. "patient level simulation"
14. "discrete event simulation"
15. "monte carlo"
16. "decision tree"
17. "quality adjusted life"
18. qaly*
19. qald*
20. qale
21. "disability adjusted life"
22. hta
23. "health technology assessment"

24. or 5-23

25. 4 AND 24

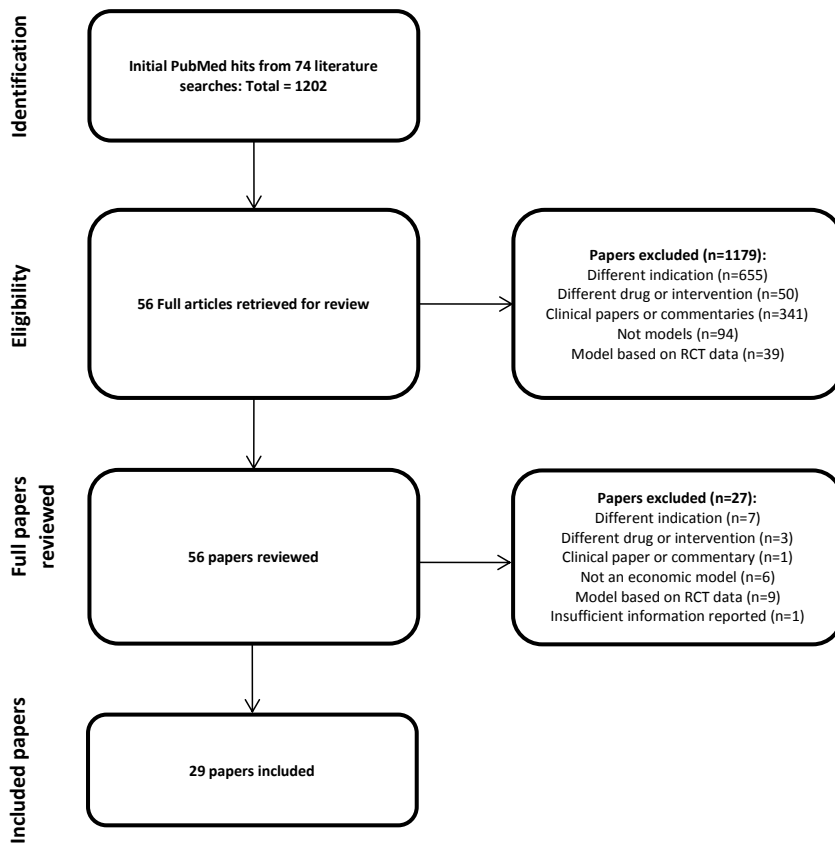**Figure 2: PRISMA diagram of economic evaluations retrieved from PubMed**

Figure 3: Taxonomy of economic modelling approaches used for estimating incremental benefit from uncontrolled clinical studies