A description of economic models constructed for pharmaceuticals granted a marketing authorisation without a randomised controlled trial by the FDA and EMA from 1999 to 2014

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The vast majority of new medicines licensed for use in the European Union and United States (the two largest single markets for pharmaceuticals), are granted a marketing authorisation on the basis of randomised controlled trials (RCTs) (Hatswell et al., 2016).

Whilst regulators are tasked with making decisions on the basis of the benefit/risk of a product, payers are generally interested in the differential efficacy a product offers, which is then linked to its cost. This may be done formally through the use of a cost per Life Year or cost per Quality Adjusted Life Year framework, or one may influence the other in a sequential process (for example assessment of clinical benefit, followed by price negotiation) (Paul and Trueman, 2001).

To estimate the additional benefits of products, modelling is generally used (Buxton et al., 1997). There are however a lack of standard methods for estimation of comparative efficacy when a study has no control arm. In this instance a comparison within the trial is not possible (due to the absence of an internal control), nor can indirect comparison techniques (Bucher et al., 1997) be used to estimate the efficacy to other comparators.

In order to understand the methods that have been used previously for treatments granted a marketing authorisation without a controlled clinical trial, we conducted a systematic review for models for all the identified products. This was published in Pharmacoconomics (Hatswell, Freemantle and Baio, 2016). In the review we identified 74 publications from a combination of PubMed entries, health technology appraisals (from NICE, SMC and AWMSG), and the ISPOR scientific presentations database. These 74 publications included 91 modelling approaches, some of which appeared in multiple formats (for example a publications a health technology appraisal submission). These 91 approaches were therefore de-duplicated, resulting in 51 individual models.

In the publication we aggregate the data from these models to generalise the approach taken (mostly commonly, an unadjusted naïve comparison of historical controls). The intention of this work however was to further describe the individual models in more detail than is available in a peer reviewed journal.

Models are presented in order of the regulatory submission of the product, and then by publication year where multiple models were identified. An index of the models included is given below.

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1. DECISION TREE OF ANAGRELIDE FOR THE TREATMENT OF ESSENTIAL THROMBOCYTOPENIA USING PATIENTS AS THEIR OWN CONTROL

The model by Bennett et al. (1999) compares the use of anagrelide to no treatment, with patients treated unsuccessfully moving on to hydroxyurea as a treatment in the US.

Efficacy data in the model was described as being taken from the FDA submission and a Phase II trial. In the data described, patients acted as their own control, with change from baseline reflecting the effectiveness of the drug assumed in the economic model.

Patients who were not successfully treated had higher rates of events linked to the disease (for example strokes). The main drivers of the model were the cost of treatments, and the lower event rates observed with the drug.

2. MARKOV MODEL OF A TREATMENT SEQUENCE BEGINNING WITH ANAGRELIDE COMPARED TO A TREATMENT SEQUENCE BEGINNING WITH HYDROXYUREA USING EXPERT OPINION ON DRUG EFFICACY

The paper (Golub et al., 2002) compares two treatment sequences – anagrelide>hydroxyurea>interferon-alpha vs. hydroxyurea>anagrelide>interferon-alpha. Patients were assumed to fail on the first two drugs after 3 months. Although the source is not referenced (though the lack of comparative data is discussed), this appears to be an assumption of equal efficacy generated by the clinicians involved.

The model itself is a Markov model, with patients eventually dying whilst stable on treatment, or remaining unresolved with a higher risk of death. As the efficacy of products was the same, the main driver for differences in the two arms of the economic model were the costs of the drugs (anagrelide being more expensive), and the risk of leukaemia with hydroxyurea.

3. NAÏVE HISTORICALLY CONTROLLED MARKOV MODEL OF ANAGRELIDE COMPARED TO INTERFERON-ALPHA OR NO TREATMENT IN ESSENTIAL THROMBOCYTOPENIA

As a part of the SMC submission for anagrelide, an economic model was submitted to the manufacturer, which is discussed in the SMC document (Scottish Medicines Consortium, 2005). The positioning was for after patients had received hydroxyurea (which a RCT had shown to be more effective since the previous models had been published).

This describes a Markov model, with data from uncontrolled studies for anagrelide, interferon-alpha, and for no treatment. Anagrelide was more expensive than the two alternatives but more effective, with the SMC ultimately recommending its use.

4. DECISION TREE MODEL OF ARGATROBAN FOR HEPARIN-INDUCED THROMBOCYTOPENIA

This decision tree compared the use of argatroban (either delivered early or late), for HIT, when compared to current clinical practice (Goldberg Arnold, Kim and Tang, 2006).

Clinical efficacy data for the drug was taken from trials, with historical control data from the hospital (which also took part in the trials for the drug) used as a comparative arm. No adjustments were
attempted for any differences at baseline between patients, and the baseline characteristics of
patients are not discussed.

5. DECISION TREE MODEL OF ARGATROBAN FOR HEPARIN-INDUCED
THROMBOCYTOPENIA INCLUDING ANTIBODY TESTING
This decision tree compared the use of argatroban (either delivered early, or late), for HIT, when
compared to current clinical practice (Patrick et al., 2007).

Clinical efficacy data for the drug was taken by pooling the trial results, with case series data from
the hospital involved in the publication used as a comparative arm. No adjustments were attempted
for any differences at baseline between patients, and the baseline characteristics of patients are not
discussed.

6. COST-UTILITY DECISION TREE OF ARGATROBAN COMPARED TO ALTERNATIVE
TREATMENTS IN HEPARIN-INDUCED THROMBOCYTOPENIA
This model appears to have been used for both SMC and AWMSG submissions and compared
argatroban to two alternatives and no treatment (AWMSG, 2012; Scottish Medicines Consortium,
2012a).

Clinical efficacy data for argatroban was taken from the historically controlled trials used for the
drug licensing (comparing argatroban to a historical case series of US patients). Comparisons were
also made to other treatments (danaparoid and lepirudin), using a naïve comparison of the
treatment arms, which was also studied compared to a historical control, as stated in the AWMSG
document:

“...clinical data in the argatroban arm of the model was a pooled analysis of the two open-
label, non-randomised, historically-controlled studies. For the danaparoid arm, a retrospective
study comparing danaparoid with historical controls was selected .... For the no further
treatment arm, the efficacy data were based on the historical controls from the argatroban
studies.”

7. COST-UTILITY DECISION TREE OF ARGATROBAN COMPARED TO ALTERNATIVE
TREATMENTS IN HEPARIN-INDUCED THROMBOCYTOPENIA
After the failure of the previous SMC submission, in this case the company, Mitsubishi Pharma
Europe, submitted a cost-minimisation analysis to the SMC (Scottish Medicines Consortium, 2013b).

In this, it was assumed that danaparoid was the relevant comparator, and after performing an
indirect comparison on historically controlled data, the company concluded that there were no
obvious differences between the drugs, and therefore, the relevant comparison was the cost of
treatment. The SMC agreed with the assessment and approved the product for use.

8. DECISION TREE OF INTRAVENOUS VERSUS ORAL BUSULFAN IN STEM CELL
TRANSPLANTATION
This poster, presented at ISPOR 2012, compared oral versus intravenous busulfan as a part of stem
cell conditioning therapy. The model was a decision tree that used results from different trials
directly as model inputs (Telléz Girón, Salgado and Soto, 2012).
9. NICE ASSESSMENT OF TEMOZOLOMIDE FOR ANAPLASTIC ASTROCYTOMA

NICE assessed temozolomide for both glioblastoma (which had an RCT) and for anaplastic astrocytoma (Dinnes et al., 2000). A model was constructed, which used data from the pivotal trial for temozolomide, and compared the results to a paper that pooled the results of 8 Phase II trials (375 patients in total).

No attempt was made to account for prognostic factors, such as the number of prior tumour recurrences, as stated by the authors of the study, “this does not provide a valid within-study comparison, it does provide some estimates by which to evaluate the potential benefit from temozolomide” (Dinnes et al., 2000, p. 32).

10. A COMPARISON OF FOSCAN PHOTODYNAMIC THERAPY WITH PALLIATIVE CARE OR CHEMOTHERAPY IN ADVANCED HEAD AND NECK CANCER

This model was described in a publication by Hopper et al., as being a comparison of palliative care, chemotherapy and photodynamic therapy (Hopper, Niziol and Sidhu, 2004). The model used trial results from the two trials directly as inputs for the three arms of the model to estimate effectiveness – one RCT of chemotherapy vs. palliative care, and the Foscan® trial. No adjustments were made for differences between trials.

The same model was also adapted to Germany, with the approach taken that the efficacy estimates were unchanged, but German costs were imputed – the authors (some of whom are authors on the publication by Hopper et al) state that “an already published model developed on the base of English data was fed with German cost-data” (Kübler et al., 2005).

11. GEMTUZUMAB OZOGAMICIN COMPARED TO A HISTORICAL CONTROL OF TREATED PATIENTS

The publication by (Lang et al., 2002) describes a model comparing gemtuzumab ozogamicin to a historical control. The data for gemtuzumab ozogamicin was taken from the three single arm clinical studies conducted in the US and Europe (n=104), whilst the historical control was taken from a case series of patients treated at Brigham Young Hospital in the US (n=22) given standard care, which in most cases was chemotherapy.

The paper does present demographic and baseline characteristics (and discuss these) for the two groups, which is unusual, and does show differences in a number of potentially important characteristics – most notably the higher duration of first remission in the gemtuzumab ozogamicin group (458 vs. 304 days), and the lower number of patients treated with gemtuzumab ozogamicin with prior myelodysplastic syndrome (0% vs. 36%), although the groups otherwise appear well balanced. Due to differences between groups, the authors attempted to adjust for baseline characteristics using multivariate regression analyses, which did alter the results of the analyses slightly.

12. ALEMTUZUMAB COMPARED TO FCR (FLUDARABINE-CHLORAMBUCIL-RITUXIMAB) COMBINATION CHEMOTHERAPY IN CLL

To compare alemtuzumab to FCR, Scott and Scott used a cost-minimisation analysis in their base case, assuming the two treatments were equally effective (Scott and Scott, 2007). The only
differences between treatments were therefore costs, driven by drug prices and monitoring/administration differences. As a result of the assumption of identical efficacy, the result of the model was that alemtuzumab was less costly to the healthcare system. Sensitivity analyses were presented using different cost inputs, where the assumption of identical efficacy was not altered.

13. IMATINIB COMPARED TO INTERFERON IN CHRONIC PHASE CML
When first licensed, imatinib had only single arm data; at this point, the drug was assessed by NICE in TA50 (Garside et al., 2002b). To calculate the cost-effectiveness of treatment compared to standard care in chronic phase CML, a historically controlled model was built on behalf of Novartis, with single arm data from imatinib compared to the results of an RCT for the main comparator, interferon-alfa, which also included another comparator, hydroxyurea. The model was described in the NICE submission (Garside et al., 2002b), and then published as a HTA report (Garside et al., 2002a), the results of the model were also reported in a subsequent NICE assessment (TA70) when an RCT of imatinib Vs. interferon became available (Dalziel et al., 2003). Finally the model was published in a peer reviewed journal by the authors in 2004 (Warren et al., 2004).

14. IMATINIB COMPARED TO HYDROXYUREA IN ADVANCED AND BLAST PHASE CML
As well as being licensed in chronic phase CML, imatinib was also licensed in advanced and blast phase CML, for which it was also assessed in NICE TA50 (Garside et al., 2002b). The cost-effectiveness of treatment was calculated by comparing the results of the imatinib trial with expert opinion on the survival of advanced and blast phase patients, who were reported to only survive for medians of 6 and 4.5 months respectively. The model was described in the NICE submission (Garside et al., 2002b) and the subsequent HTA report (Garside et al., 2002a). In 2003, the model was then published by the authors (Gordois et al., 2003).

15. IMATINIB COMPARED TO BEST SUPPORTIVE CARE IN GIST USING HISTORICAL CONTROLS
This model compared imatinib to best supportive care in GIST. Although 12 published historical controls were identified by the company, only one was used, with a second used in sensitivity analysis – the rationale given for the choice of study was that patients were confirmed to be CD117 positive, the specific mutation for which imatinib was licensed. The model was used for NICE TA 86 (Wilson et al., 2003) and then published as a HTA report (Wilson et al., 2005). It was later published by the authors, using US costs and historical control data from the sensitivity analysis and a more recently published historical control (Huse et al., 2007).

16. IMATINIB COMPARED TO BEST SUPPORTIVE CARE IN GIST USING CASE SERIES DATA
This model was presented at the first ISPOR Asia-Pacific Conference and compares imatinib with best supportive care (De Abreu Lourenco and Wonder, 2003). Data for imatinib was taken from an on-
going clinical trial, with data for best supportive care taken from a case series at a different institution. No baseline characteristics for the two datasets were reported.

17. CETUXIMAB IN METASTATIC COLORECTAL CANCER, COMPARED TO USUAL CARE USING ASSUMPTIONS REGARDING THE EFFECTIVENESS OF CETUXIMAB

Cetuximab was assessed by NICE in TA118, with Merck submitting this model, and later, the authors published it in a peer reviewed journal (Merck Pharmaceuticals, 2005; Starling et al., 2007).

To estimate the overall survival gain from cetuximab usage, parametric curves were fitted to the cetuximab data, and then extrapolated beyond the initial time period. To estimate the effectiveness of BSC, the hazard ratio was taken from a study in a different setting of head and neck cancer (comparing irinotecan to best supportive care) and applied to the cetuximab results. Implicitly this assumes the benefit of cetuximab is the same as irinotecan and that hazard ratios are equal between different lines of treatment.

18. CETUXIMAB COMPARED TO USUAL CARE USING IN METASTATIC COLORECTAL CANCER WITH HISTORICAL CONTROLS

In assessing the cost-effectiveness of cetuximab in head and neck cancer, the evidence review group did not think the estimates provided by Merck to be credible, and instead searched for suitable historical controls. Three of these were identified from previous clinical trials, with estimates of cost-effectiveness made using naïve comparisons of survival between the cetuximab study and each of the three historical controls identified. For each survival curve, a parametric curve was fitted, and the estimates QALYs gained from each arm calculated, along with the costs.

The results were reported in the evidence review group report for TA118 (Tappenden et al., 2006), and subsequently in a HTA report (Tappenden et al., 2007).

19. CETUXIMAB COMPARED TO USUAL CARE IN METASTATIC COLORECTAL CANCER USING THRESHOLD ANALYSIS

In NICE TA118, after noting the limitations of the evidence base, the evidence review group performed a threshold analysis of the incremental survival benefit needed for cetuximab to be cost-effective at different willingness to pay levels (Tappenden et al., 2006). This was done by using the extrapolated survival curve from the cetuximab study, and then calculating what overall survival would have needed to be for the control arm, and later reported in a HTA report (Tappenden et al., 2007).

Although exact figures for the benefit of the drug were not provided, it does appear to have featured prominently in the committee’s decision making. For cetuximab to be cost-effective at a willingness to pay of £20,000 per life year (when the value usually used in decision making is £20,000 to £30,000 per Quality adjusted Life Year), the drug would have needed to have added 0.7 life years over best supportive care. Given that cetuximab was estimated to provide 0.79 life years, this would have meant the mean survival on best supportive care would have needed to be 0.09 life years, or approximately 1 month.
20. CETUXIMAB COMPARED TO USUAL CARE USING IN METASTATIC COLORECTAL CANCER USING CASE SERIES DATA

Annemans et al. compared cetuximab to usual case using case series data (Annemans et al., 2007). In order to generate a matched case series, the investigators conducted a chart review at three hospitals in Belgium, France and Italy, who were involved in the cetuximab study.

Patients who would have been eligible for the cetuximab study, but who were treated outside of the enrolment period were included in the hope this would create a matched cohort. The survival of these patients was then compared to the survival from the pivotal study to give an estimate of the overall survival benefit of cetuximab.

21. TRABECTEDIN FOR THE TREATMENT OF STS USING A HISTORICAL CONTROL AND DISEASE RESPONSE

A Markov model was constructed for trabectedin compared to end stage treatment using the data from the clinical study of trabectedin and patient-level data from previous clinical trials conducted by the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group.

Patients treated with trabectedin went to either stable or progressive disease and then followed transition probabilities related to these, whilst patients given end stage treatment died at the rate taken from the patient-level data.

The model was presented at the ISPOR 12th Annual European Congress in 2009 (Soini, García San Andrés and Joensuu, 2009) before being published in 2011 (Soini, Garcia San Andres and Joensuu, 2011). It was also used for submissions to the AWMSG (AWMSG, 2008) and the SMC (Scottish Medicines Consortium, 2008b).

22. TRABECTEDIN FOR THE TREATMENT OF STS USING A HISTORICAL CONTROL AND PARAMETRIC CURVE FITTING

Trabectedin was assessed by NICE for the treatment of STS in TA185, with the company creating a model for submission to estimate the cost effectiveness of the drug. For comparative data, the model used data from the licensed dose of trabectedin from the clinical study and compared this to a set of historical controls. In this case the historical controls consisted of four pooled trials published by the European Organisation for Research and Treatment of Cancer – Soft Tissue and Bone Sarcoma Group. The data from the historical controls were then adjusted to match the control group using a regression with dummy variables for performance status, histopathology of disease, age, and gender – this improved the estimated survival of best supportive care slightly.

The model was used in a submission to NICE (Simpson, Rafia and Stevenson, 2009), and later published in a HTA report (Simpson et al., 2010) and discussed in a review paper (Rafia et al., 2013). In addition to the NICE appraisal, the model was also used in two SMC submissions, first without controlling for differences between baseline characteristics (Scottish Medicines Consortium, 2010b), and then in a resubmission, where the price of the drug was also reduced (Scottish Medicines Consortium, 2011).
23. **TRABECTEDIN FOR THE TREATMENT OF STS USING AN ASSUMPTION OF EQUAL POST-PROGRESSION SURVIVAL BETWEEN TREATMENTS**

Several years after trabectedin was licensed, pazopanib was licensed in a similar positioning, with an economic model constructed by GlaxoSmithKline comparing pazopanib to best supportive care, trabectedin, ifosfamide and gemcitabine/docetaxel combination.

In the model, the survival for pazopanib and best supportive care were taken from an RCT conducted by GlaxoSmithKline, whilst other comparisons were made by taking the pre-progression data from clinical trials for each drug and assuming the post-progression period was identical between treatments. No adjustments were made for differences in patient characteristics.

The model was constructed based on UK costs (Amdahl et al., 2014), and later adapted to Spain (Villa et al., 2014), although no changes were made in the approach to modelling effectiveness.

24. **MARKOV MODEL OF CLADRIBINE COMPARED TO PENTOSTATIN FOR THE TREATMENT OF HAIRY CELL LEUKAEMIA**

This model was constructed by Guest et al., (Guest et al., 2009) to compare Cladribine and pentostatin in the first-line treatment of HCL. Efficacy for the two drugs was modelled using comparisons of the trial data for the drugs, although this was adjusted to ensure the efficacy rates were for comparable patient groups.

25. **SURVIVAL MODEL OF GEFITINIB COMPARED TO BEST SUPPORTIVE CARE IN NSCLC**

This model was presented at ISPOR in 2004 and compares gefitinib to best supportive care using data from clinical trials. The gefitinib data were taken from the (uncontrolled) clinical study used for regulatory filings, whilst the data for best supportive care arm were taken from an RCT of a different drug (Ratcliffe, Beard and Wolowacz, 2004).

26. **COST-EFFECTIVENESS OF BORTEZOMIB COMPARED TO BEST SUPPORTIVE CARE IN ADVANCED MULTIPLE MYELOMA**

Bortezomib was initially licensed on the basis of uncontrolled clinical data; however, the majority of models constructed around its effectiveness were constructed later once an RCT was available. For this, the only model constructed based on uncontrolled data, data from the clinical study of bortezomib was compared to expert opinion on the outcomes in untreated patients (Mehta, Duff and Gupta, 2004). In this case the expert opinion was elicited via the use of Delphi panels, with three comparisons made; all patients, patients treated with thalidomide (a recognised early treatment in multiple myeloma), and patients not treated with thalidomide.

27. **CLOFARABINE COMPARED TO BEST SUPPORTIVE CARE IN ALL**

After licensing, submissions were made to the SMC and the AWMSG for clofarabine, in which a model was used to compare it to best supportive care. The model used the same data as the regulatory submission for clofarabine, comparing the outcomes of the single arm study of clofarabine naively to a historical control generated from two observational registries, and only patients who would had met the entry criteria for clofarabine were included (Scottish Medicines Consortium, 2006; AWMSG, 2007a).
28. **MARKOV MODEL OF NELARABINE COMPARED TO CLOFARABINE AND BEST SUPPORTIVE CARE IN ALL**

Soon after clofarabine was licensed, Nelarabine was also licensed for the same patient population, also with single arm data. The manufacturer, GlaxoSmithKline, also made submissions to the SMC and the AWMSG. In their model, described as a Markov model, patients were either treated or received best supportive care, and then went on to receive stem cell transplant, if a responder.

The data for Nelarabine was taken from the trials that were conducted (some in adults and some in children), and included only patients treated with the licensed regimen. In the model the same approach was also used to model clofarabine, using clinical trial results and BSC (where no patients were assumed to receive a stem cell transplant, as response was assumed to be 0%). The high level of uncertainty in the analysis was noted by both the SMC and the AWMSG (Scottish Medicines Consortium, 2008a; AWMSG, 2009).

29. **BETAINE PLUS STANDARD CARE COMPARED TO STANDARD CARE FOR THE TREATMENT OF HOMOCYSTINEUREA**

To submit to the SMC, the manufacturer of betaine built a cost-effectiveness model using the same data as the regulatory submission. The decision tree model used the rate of vascular events from the clinical study of betaine plus standard care and compared this with the rate seen on standard care in a published observational study (Scottish Medicines Consortium, 2010a).

30. **ALGLUCOSIDASE ALFA FOR THE TREATMENT OF POMPE DISEASE MODELLLED USING MATCHED REGISTRY DATA**

This economic model was described in an SMC submission from 2007 (Scottish Medicines Consortium, 2007a) and then described in a publication in 2012 (Castro-Jaramillo, 2012).

The approach used to model the drug was to use the data from the clinical trial, with expert opinion taken regarding how this should be extrapolated. The comparator, no treatment, was modelled using registry data, with only those matching the characteristics included in the model.

31. **ALGLUCOSIDASE ALFA FOR THE TREATMENT OF POMPE DISEASE MODELLED USING MATCHED REGISTRY DATA**

As a part of the Dutch reimbursement system, drugs can be offered access to the market, providing data is collected on their use, which can later be used to inform the cost-effectiveness of the drug in practice. In the economic model, data from such a scheme was included.

To model to the effectiveness of alglucosidase, clinical trial data was used (n=39), and combined with data from patients treated with the drug at the Erasmus medical centre (n=20). This was compared to two international registry studies of survival with Pompe disease. Beyond the end of the available data, survival was extrapolated for both arms using parametric curve fits (Kanters et al., 2014).
32. **SUNITINIB COMPARED TO BEST SUPPORTIVE CARE IN THE TREATMENT OF SECOND-LINE METASTATIC RENAL CELL CARCINOMA, USING CASE SERIES DATA**

After sunitinib was licensed, the manufacturer, Pfizer, used an economic model to submit to the SMC that was also adapted to several different countries. The model compared the results observed with sunitinib (and extrapolated from a 2-year trial, to a 6-year horizon) to the outcomes reported in a published case series and Medicare data (Scottish Medicines Consortium, 2007b).

The model is described in the SMC submission, and was adapted to Belgium (Van Nooten *et al.*, 2007) and Spain, where only the comparison with Medicare data was presented, both as an ISPOR poster (Aiello *et al.*, 2007) and in a peer reviewed journal (Paz-Ares *et al.*, 2010).

33. **SUNITINIB COMPARED TO ACTIVE THERAPIES IN SECOND LINE METASTATIC RENAL CELL CARCINOMA USING EXPERT OPINION OF DRUG EFFECTIVENESS**

At the same conference estimates were presented by Pfizer, a poster by the MD Anderson Cancer Center in Texas was also presented showing the assumptions that were used regarding the effectiveness of each drug that was available. The approach taken does not appear to be highly evidence based, with only expert opinion cited as the reason sunitinib was judged to be better than other treatments. The results of the analysis were then used to support the conclusion that “Sorafenib and sunitinib offer a superior treatment option at a lower cost and potential for improved revenue” (Smith and Arbuckle, 2007).

34. **SUNITINIB COMPARED TO BEST SUPPORTIVE CARE IN SECOND LINE METASTATIC RENAL CELL CARCINOMA USING LOCALLY COLLECTED CASE SERIES DATA**

This model was built around the same time as those presented by Pfizer and the MD Anderson Center, but appears much more comprehensive. The results from a Phase II single arm study on sunitinib were compared to medical records of 39 patients from Finnish hospitals (the setting for the analysis was Finland). Patients who would have been unsuited for the sunitinib trial (and therefore not necessarily comparable) were not included in the case series. A parametric curve was then fitted to this case series data.

The model was initially presented at ISPOR Dublin in 2007 (Purmonen *et al.*, 2007) before being published in a peer reviewed journal (Purmonen *et al.*, 2008).

35. **DASATINIB COMPARED TO IMATINIB IN ACCELERATED PHASE CML**

As dasatinib was licensed for chronic, accelerated, and blast phase CML, the manufacturer, BMS, built a model that contained all disease stages through which patients progress. In the chronic phase, results from a RCT of dasatinib vs. imatinib, whereas in the accelerated phase, where only single arm data is available for both drugs, the results of trials for both treatments were extrapolated using curve fits and then used directly in the model.

This approach was taken in the SMC submission (Scottish Medicines Consortium, 2007) and the AWMSG submission (AWMSG, 2007b), followed by the NICE submission (Loveman *et al.*, 2011).

36. **DASATINIB COMPARED TO IMATINIB IN BLAST PHASE CML**
This model was based on the same model as the dasatinib chronic and advanced phase models. Though the inputs were different, the principle was the same – parametric curve fitting was performed to the results of the (single arm) dasatinib and imatinib trials, and the results of these curve fits used directly in the model.

This model was then used to generate estimates in the SMC submission (Scottish Medicines Consortium, 2007), the first AWMSG submission (AWMSG, 2007b), the second AWMSG submission ((AWMSG, 2007), and the NICE submission (Thompson Coon et al., 2009; Loveman et al., 2011).

37. **DASATINIB COMPARED TO IMATINIB IN PH+ ALL**
This model was described in an AWMSG submission as being based on the same model as the blast phase CML model submitted by BMS, an indication that was also assessed in this appraisal – the clinical study in which data were generated also included both types of patients. The difference to the dasatinib blast phase model appears to be that the clinical data from the Ph+ patients extrapolated (via parametric curve fitting) for dasatinib and imatinib, although the remainder of the data remains the same including utilities and resource use (AWMSG, 2007).

38. **BORTEZOMIB COMPARED TO CHEMOTHERAPY IN MANTLE CELL LYMPHOMA**
This model was presented at ISPOR 2009 and compares the results of the bortezomib study to those from a trial of chemotherapy. The results of both trials were extrapolated, with no adjustments made to trial data (Yoong, Attard and Sehn, 2009).

39. **NILOTINIB COMPARED TO HIGH-DOSE IMATINIB AND BEST SUPPORTIVE CARE IN CML USING A NAÏVE COMPARISON OF TRIAL RESULTS**
In this model, the results of the imatinib and nilotinib studies were extrapolated by converting trial results to a monthly mortality rate, which was then compared to a 5-year survival curve for best supportive care from a clinical trial in the literature. Patients were assumed to spend the last portions of their disease in accelerated and blast phases of the disease, which was assumed to be the same for all treatments.

This model was submitted by Novartis to the SMC (Scottish Medicines Consortium, 2008) and again to NICE as a part of NICE TA241, an MTA in second-line CML (Loveman et al., 2011).

40. **HIGH-DOSE IMATINIB, NILOTINIB, DASATINIB, AND STANDARD CARE IN CHRONIC PHASE CML USING SURROGATE RESPONSE RATES**
This model was constructed by the manufacturer of dasatinib, BMS, for NICE TA241. Although dasatinib at this point in time had a comparative trial, this was not the case for nilotinib – in this case a comparator. The approach used to modelling survival was based on the surrogate outcome of major cytogenetic response. This was then used to predict survival based on the survival observed in responders and non-responders in separate trials (Taylor et al., 2011).

41. **HIGH-DOSE IMATINIB, NILOTINIB, DASATINIB, AND STANDARD CARE IN CHRONIC PHASE CML USING EXPERT OPINION AND SURROGATE RESPONSE RATES**
This model was constructed by the evidence review group in TA241 and used the same approach to modelling survival as the Taylor et al., model from BMS (Taylor et al., 2011)— estimating survival
based on that observed in responders and non-responders in separate trials and assuming similar values would be achieved by the new drugs (Loveman et al., 2011).

In the model, using the response rates observed with nilotinib gave an estimate of patients remaining on treatment for 4 years more than dasatinib (a drug from the same class). As this was judged to be implausible, expert opinion was used that the progression free survival of the drugs would be the same. Other subtle differences were also included in the evidence review group model compared to the model submitted by BMS, mostly surrounding cost estimates.

42. **TUCOFERSOLAN COMPARE TO USUAL CARE FOR CHRONIC CHOLEOSTASIS**

After initially not submitting an economic evaluation to the SMC, this model was submitted in a re-submission. The structure of the model was a short-term decision tree, after which patients would go into Markov models depending on their resulting health state. The model was then informed by the trial, where only 2 patients with the relevant subtype of disease were included. The effectiveness of the comparator was then assumed to be 98% that of tocofersolan (Scottish Medicines Consortium, 2012b).

43. **OFATUMUMAB COMPARED TO BEST SUPPORTIVE CARE IN DOUBLE REFRACTORY CLL USING A COMPARISON OF ALL PATIENTS TO NON-RESPONDERS**

This is a model which I led whilst working at GSK. To create a control arm for best supportive care, the model compares all patients with double refractory CLL, to patients treated, but not achieving a response to ofatumumab. The assumption made is that had patients not achieved a response with ofatumumab, they would have had a similar prognosis to non-responders. This comparison was achieved by fitting a Weibull curve to responders and by performing a Cox regression to account for differences in baseline characteristics.

The assumptions implicit in the model were that response was a random occurrence and not linked to any particular patient characteristic (which would result in bias in favour of the drug) and that non-responders received no benefit from the drug at all (which would result in bias against the drug).

The model was submitted to NICE as a part of TA202 (Hoyle et al., 2010), as a HTA report (Hoyle et al., 2011), to the SMC (Scottish Medicines Consortium, 2010) and presented at ISPOR 2010 (Batty et al., 2010). Subsequently the curve fits and approach used was reanalysed using Bayesian methods, finding that these did not change the result of the original analysis (Almond et al., 2013).

44. **CARGLUMIC ACID COMPARE TO USUAL CARE FOR THE TREATMENT OF HYPERAMMONAEMIA USING CASE SERIES DATA**

To compare carglumic acid to usual care, the manufacturer of carglumic acid constructed a model based on a 2-year decision tree, with a Markov model then extrapolating results over a lifetime horizon. Data from carglumic acid were taken from the clinical trial and compared to outcomes from an Italian case series, with expert opinion used to bridge any gaps (Scottish Medicines Consortium, 2013a).
45. **PEGASPARGASE COMPARED TO ASPARAGINASE IN ADULT ALL USING A COST-MINIMISATION MODEL**

The publication by Peters et al. describes a cost-minimisation model to compare two forms of asparaginase, with pegaspargase having lower hypersensitivity reactions but costing more (Peters et al., 1995). Cost-minimisation implicitly assumes the two treatments are equally as efficacious, despite differences in serum levels and point estimates of survival in clinical trials.

46. **BRENTUXIMAB COMPARED TO STEM CELL TRANSPLANT AND STANDARD OF CARE) IN HODGKIN'S LYMPHOMA USING AN ADJUSTED COMPARISON OF TRIAL RESULTS**

Although only presented in poster format, this is arguably one of the most comprehensive assessments of single arm data performed. The model compared brentuximab vedotin overall survival to that of untreated patients (Woods et al., 2013).

A systematic review for the efficacy of the comparators (chemotherapy and stem cell transplant) was performed, and 31 studies were found. Two large studies were then selected as being representative of the two comparators and compared to the results of the brentuximab vedotin trial.

In an additional step the estimated efficacy of other treatments was adjusted to account for differences in baseline characteristics, which increased the estimated survival of patients treated with chemotherapy, and particularly those treated with stem cell transplantation. This adjustment is reproduced in Figure Error! No text of specified style in document.-1.

![](image)

Figure Error! No text of specified style in document.-1: Reproduction of Figure 3 from Woods et al. (2012) – Adjusted and unadjusted overall survival in Hodgkin's lymphoma

47. **DEFIBROTIDE COMPARED TO BEST SUPPORTIVE CARE FOR TREATMENT OF SEVERE HEPATIC VENO-OCLUSIVE DISEASE**
The model submitted to the SMC for defibrotide uses the results of the clinical trial outcomes for defibrotide and compared these to the results of a historical control (selected patients from a case series). After one year of treatment, patients in both arms were assumed to follow the survival trajectory of patients with AML (Scottish Medicines Consortium, 2014).

48. **BOSUTINIB FOR THE TREATMENT OF CHRONIC PHASE CML USING CYTOGENETIC RESPONSE RATES**

This is a model I led on, on behalf of Pfizer, the manufacturer of bosutinib.

In the model, to estimate the survival for patients treated with either bosutinib or hydroxyurea, the cytogenetic response rates from each trial were used to generate estimates survival, based on the survival observed in a previous trial. This was the approach used in the evidence review group model of imatinib, dasatinib and nilotinib in second-line CML (Loveman et al., 2011) and that was also used in first-line CML (Hoyle et al., 2012).

The model was submitted to NICE (Pfizer UK, 2013), subsequently appearing in the evidence review group report (Hoyle et al., 2013) and the HTA report (Hoyle et al., 2013), then submitted to the SMC (Scottish Medicines Consortium, 2013) and described in an oral presentation at ISPOR Europe 2013 (Pennington, Hatswell and Clifton-Brown, 2013).

49. **BOSUTINIB FOR THE TREATMENT OF CHRONIC PHASE CML USING A CUMULATIVE TIME ON TREATMENT APPROACH**

On reviewing the manufacturer model for NICE TA299, the evidence review group proposed an alternative method for estimating the survival and quality of life gain of bosutinib, which they deemed the cumulative approach.

As patients discontinuing bosutinib would then receive the current standard of care, patients were assumed to have the costs and benefits of bosutinib, and then afterwards receive standard of care, and the same duration of benefit. The assumptions implicit in the approach are that there is no effect of bosutinib after patients come off treatment, and that they would receive the same level of benefit from current standard of care, despite having tried (and failed) an additional line of chemotherapy.

The approach was described in the evidence review group report (Hoyle et al., 2013), and subsequently in the HTA report (Hoyle et al., 2013) and in an oral presentation at ISPOR Europe 2013 (Pennington, Hatswell and Clifton-Brown, 2013).

50. **BOSUTINIB COMPARED TO STANDARD CARE FOR THE TREATMENT OF ACCELERATED PHASE CML**

As well as chronic phase CML, bosutinib was licensed in advanced phase CML. To model the effectiveness of bosutinib, a parametric curve was fitted to the survival of bosutinib-treated patients, with the resulting area under the curve compared to expert opinion on the survival of advanced phase patients given only standard care (8 months in the accelerated phase, then 6 months in the blast phase).
The approach was described for the NICE submission in the Pfizer submission for TA299 (Pfizer UK, 2013), an evidence review group report (Hoyle et al., 2013) and a HTA report (Hoyle et al., 2013). It was also submitted to the SMC (Scottish Medicines Consortium, 2013).

51. BOSUTINIB COMPARED TO STANDARD CARE FOR THE TREATMENT OF BLAST PHASE CML

The model for bosutinib in blast phase CML was very similar to that for the accelerated phase. Patient-level data from bosutinib treated patients had a parametric curve fitted to extrapolate survival beyond the 2-year trial period. The results of this curve fitting were then compared to expert opinion on the survival of blast phase patients given only standard care (6 months).

The approach was described for the NICE submission in the Pfizer submission for TA299 (Pfizer UK, 2013), an evidence review group report (Hoyle et al., 2013) and a HTA report (Hoyle et al., 2013). It was also submitted to the SMC (Scottish Medicines Consortium, 2013).


Scottish Medicines Consortium (2005) ‘Re-submission - Anagrelide 0.5mg capsule (Xagrid)’. Scottish Medicines Consortium.


Scottish Medicines Consortium (2012b) 'Tocofersolan, 50mg/mL (corresponding to 74.5 IU tocopherol) oral solution (Vedrop®) SMC No. (696/11)’. Scottish Medicines Consortium. Available at: https://www.scottishmedicines.org.uk/files/advice/tocofersolan_Vedrop.pdf.


