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Which Factors Enhance Positive Drug Reimbursement Recommendation in Scotland? A Retrospective Analysis 2006–2013

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ABSTRACT

Objectives: To identify the factors that influence the Scottish Medicines Consortium (SMC) in deciding whether to accept pharmaceutical technologies for use within the Scottish health care system. **Methods:** A database of SMC submissions between 2006 and 2013 was created, containing a range of clinical, economic, and other factors extracted from published health technology assessment reports. A binomial outcome variable was used, defined as the decision to "accept for use" or "not recommend" a technology. Univariate and multivariate analyses were conducted to assess the impact by means of odds ratios (ORs) of the submitted evidence on the recommendation decision. **Results:** Out of 463 applications, 265 were accepted for use (57%) and 198 (43%) were not recommended for use within National Health Service Scotland. Univariate analyses showed that 13 variables significantly affected the SMC decision. Of these 13 variables, 7 variables were shown to have a meaningful impact in the multivariate analysis. Four of these concerned the outcome of cost-effectiveness analyses; the fact that a submission was supported by a cost-minimization analysis was the strongest positive variable (OR = 10.30) and a submission showing a product not being cost-effective (i.e., incremental cost-effectiveness ratio above £30,000/quality-adjusted life-year gained) was the strongest negative predictor (OR = 0.47). The other variables concerned whether the submission was related to a product indicated for a nervous system disease (OR = 0.41), whether it was indicated for nonchronic use (OR = 1.66), and whether the submission was performed by a big company (OR = 2.83). **Conclusions:** This study demonstrated that the outcome of cost-effectiveness analyses is an important factor affecting the SMC's reimbursement recommendation decision.

Keywords: decision making, health technology assessment, reimbursement, Scotland.

Introduction

Given limited health care resources and rising expenditures on pharmaceuticals, policymakers are increasingly confronted with the challenging task to improve patient outcomes and reimburse new pharmaceutical interventions [1]. In several countries, including England and Wales, Scotland, The Netherlands, Belgium, Canada, Australia, and Sweden, health technology assessment bodies have been set up to advise on whether health care interventions should be recommended for public reimbursement [2–4]. Most health technology assessment bodies consider evidence not only on clinical effectiveness and safety but also on various other factors such as cost-effectiveness and budgetary impact. With more and more national health authorities requesting health economic evaluation for their reimbursement decisions, the significance of economic factors in the advisory or decision-making process has increased.

The importance of individual components of evidence, for example, clinical outcomes, disease characteristics, and health economic outcomes, which are submitted to local health authorities as part of a reimbursement dossier, however, is generally not described. There is an exception for the National Institute for Health and Care Excellence (NICE) in England and Wales, which uses the incremental cost-effectiveness ratio (ICER) threshold of £20,000 to £30,000 per quality-adjusted life-years (QALYs) gained. Yet, NICE appraisals suggest that various factors are taken into account and a drug can be positively assessed even if the ICER exceeds that threshold. More precisely, as the ICER of an intervention increases in the range of £20,000 to £30,000 per QALY gained, the NICE Committee's judgment about the acceptability of the technology as an effective use of National Health Service (NHS) resources will specifically take account of other factors, such as the degree of certainty around the ICER, innovative nature of the technology, inadequately captured quality-of-life

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benefits, and potential "life-extensive" nature of the treatment under assessment [5]. Nevertheless, most countries have not set a formal cost-effectiveness threshold for reimbursement; therefore, it is not clear how the economic results relate to other factors in the decision or advisory process.

A number of quantitative studies have been previously conducted to investigate what factors are influential and how much impact these factors have on reimbursement decisions in specific countries, including England and Wales [6–10], The Netherlands [11], and Australia [12,13]. To our knowledge, no study has been conducted for the Scottish Medicines Consortium (SMC).

Within the National Health Service for Scotland (NHS Scotland), 14 geographically based local NHS boards and a number of National Special Health Boards are responsible for the provision of health care [14]. The SMC, a consortium of NHS Scotland, was established to benefit patients by providing NHS boards and their Area Drug and Therapeutics Committees with a single source of advice about the value of each new medicine and the patients for whom it would be most beneficial [14,15]. In particular, the SMC advises NHS Scotland whether a newly licensed drug should be reimbursed on the basis of the value for money it represents to NHS Scotland. The SMC provides a central reimbursement recommendation as soon as possible after the launch of the product, which is based on the clinical and economic evidence provided by the manufacturer [15,16]. The advisory process involves the assessment of both clinical and economic evidence as submitted by the manufacturer by lead clinicians, pharmacists, and health economists together with representatives of health boards, the pharmaceutical industry, and patient associations [15,16]. The SMC can positively assess and accept a drug for either routine or restricted use, or, alternatively, it can suggest rejection of public funding of the medicine [16]. On completion of the SMC assessment process, its advice for NHS Scotland is published and the final formulary inclusion decision is made by the local health boards using this advice. It is important to note that NHS boards will consider all SMC-accepted advice as a matter of course but can still decide not to include such medicines on their own local formulary, that is, where the medicine does not represent sufficient added benefit to other medicines already on the formulary for the same indication [15]. Detailed information is available on the organization's Web site (www.scottishmedicinesconsortium.com) [15].

Arguably, Scotland is often one of the first European countries where manufacturers file a submission dossier requesting public reimbursement for their product. Manufacturers submit their evidence to the SMC before they submit it to the relevant health technology assessment body of England and Wales, NICE [14,17]. It seems that SMC's assessment of evidence approach is closer to that used elsewhere in Europe and its activities are to a large extent complementary to the ones of NICE [14,18]. The SMC advisory process is transparent in the sense that all decisions and argumentations are published on SMC's Web site since 2002 [15]. Hence, feedback of the SMC on a submission might have implications on decisions of other health authorities and affect the product's pricing in Europe on grounds of the reference pricing system [19].

The purpose of the present study was to investigate the weight that different pieces of evidence, submitted to the SMC for reimbursement assessment, have on the final recommendation decision by the SMC.

Methods

A comprehensive database was created including information from all drug appraisals performed by the SMC between January 2006 and July 2013. They year 2006 was chosen as the starting point for the SMC data collection for this analysis because this year was considered to be the one in which SMC's role was strengthened and evolved into the one that it currently has [20]. The SMC publishes the reimbursement recommendation itself together with wide-ranging details on the submission in a standardized format that is accessible to the general public [15]. Information from "full submissions" (i.e., submissions for the first time) as well as resubmissions was included in the database. Appraisals that were labeled as "abbreviated submission" or "IRP guidance (Independent Review Panel)" were not considered for this research because they provided limited information on the submitted evidence.

From each appraisal, numerous variables were extracted. These included the opinion of the SMC (a product being accepted for routine or for restricted use was treated as one category) and several factors that were grouped into five main classes: clinical evidence, therapeutic indication–related information, disease characteristics, health economic evidence, and other relevant information. Altogether, the data set included 20 variables that were thought to potentially influence the recommendation of the SMC. Table 1 presents these variables together with their definitions and possible sets of values.

The extent to which the submitted evidence influences the final recommendation of the SMC was assessed by odds ratios (ORs) estimated from binomial logistic regression analyses. The STATA software was used [22]. Analyses took place in two phases; in the first phase, univariate logistic regression models were set up to examine the relationship between each individual independent variable (explanatory variables) and the decision of the SMC (dependent variable), defined as "to accept" or "not to recommend" a product for use within NHS Scotland. In the second phase, a multivariate logistic regression analysis was undertaken to assess how the presence of multiple factors influences the recommendation of the SMC. The explanatory variables that indicated a statistically significant relationship with the dependent variable in univariate analyses (i.e., $P \leq 0.05$) were included in the multivariate model. If for a multinomial explanatory variable at least one category was significantly associated with the outcome, then the whole multinomial variable was considered for the multivariate analysis. Missing information led to the exclusion of an observation from regression analyses.

Variable selection in the multivariate logistic regression model was performed using a backward elimination procedure [23]. Specifically, the backward elimination procedure started with all considered variables (i.e., variables with a P value of <0.05 in the univariate analysis), tested the deletion of each variable for model improvement (exit criterion was a P value of >0.05), and repeated this process until no further improvement was possible. The backward elimination algorithm was chosen for this study because it is a commonly used and well-accepted method for variable selection and because it is less adversely affected by correlations among explanatory variables than are other methods (e.g., forward selection and stepwise regression methods) [23]. The predictive power of the multivariate model was assessed by the area under the receiver operating characteristic curve.

For the base-case analysis, resubmissions were treated as original submissions. One could argue, however, that the result of a resubmission was not independent from that of the original submission because at the resubmission the manufacturer could address the critique expressed by the SMC during the first assessment and could eventually increase the chance of a positive recommendation. If this is true, depending on the strength of this correlation and the number of resubmissions, standard errors of the analyses may not be correct even though parameter estimates would be still unbiased. To acknowledge

Table 1 – Description of variables included in the SMC data set.

Variable	Definition	Explanation
Clinical evidence		
Type of compound	$D = 0$; Chemical $D = 1$; Biological	This variable indicated whether the entity of the drug is biological or chemical. Chemical entities contain an active moiety (molecule or ion), whereas biological products are composed of cellular or tissue-based products (e.g., proteins, antibodies, and viruses).
Control arm in clinical trial	$D = 0$; Placebo $D = 1$; Active $D = 2$; Uncontrolled	This variable indicated the type of control arm used in the clinical trial that backed the submitted clinical evidence in the submission. A trial could be active-controlled, placebo-controlled, or uncontrolled (i.e., single-arm trial). If more than one trial was reported, the one given as the pivotal trial was extracted and used. An active-controlled trial was preferred over a placebo-controlled study in case more studies were reported and in case none of them was marked as the pivotal one. If more than one active-controlled trial was reported, the one used in the pharmacoeconomic analysis section of the SMC document was chosen to be extracted.
Clinical trial's primary end point	$D = 0$; Lifesaving/hard end point $D = 1$; Surrogate end point	A trial was considered to have a potentially lifesaving/hard end point if the primary outcome was to prevent an event (e.g., death or stroke). Surrogate end point has been defined as "a biomarker intended to substitute for a clinical end point" (e.g., lowering blood pressure). The clinical primary end point of the chosen clinical trial, as described above "Control arm in clinical trial," was extracted and used.
Efficacy profile	$D = 0$; Trial was uncontrolled $D = 1$; Superior efficacy vs. active comparator $D = 2$; Superior efficacy vs. placebo $D = 3$; Nonsuperior efficacy vs. active comparator $D = 4$; Nonsuperior efficacy vs. placebo	A drug was considered to have superior/inferior efficacy if the new drug was demonstrated to have a statistically significantly better/worse efficacy profile than the comparator regarding the primary trial end point. If the trial was uncontrolled, no comparator was used.
Safety profile	$D = 0$; Nonsuperior safety (similar safety) $D = 1$; Superior safety $D = 2$; Inferior safety $D = 3$; Trial was uncontrolled	A product was considered to have a superior/inferior safety profile than its comparator if it was associated with significantly less/more severe adverse effects than its comparator. If the trial was uncontrolled, no comparator was used.
Indication-related evidence		
Therapy type	$D = 0$; Drugs meant for monotherapy $D = 1$; Drugs meant for combination therapy	A new drug can be administered as a combination treatment, i.e., in combination with another drug, or as monotherapy, i.e., administered alone.
Treatment line	$D = 0$; First-line treatment drug $D = 1$; Subsequent treatment line drug	A drug was considered to be a first-line treatment if it was to be the first treatment given to the patient after the diagnosis. The drug was considered as later treatment line if it is indicated to be administered as a subsequent treatment line, i.e., after the failure of the previous treatment option(s).
Chronic use	$D = 0$; Drug meant for chronic use $D = 1$; Drug not meant for chronic use	Chronic use indicated that a drug is indicated for the treatment of a chronic disease and no restrictions to the treatment duration were defined (i.e., treatment is administered until cure, discontinuation, or death). In contrast, a product is not indicated for chronic use if it is indicated for the treatment of acute events or a definite treatment duration is predefined.
Competition	$D = 0$; Two or more competitors $D = 1$; One competitor $D = 2$; No competitors	No competitor in the market was considered if the drug of interest was to be the first reimbursed treatment for the specific indication. One or more competitors indicated if there were already one or more treatments reimbursed for that indication.
Disease characteristics		
Orphan indication	$D = 0$; Orphan indication $D = 1$; No orphan indication	Orphan indication was given to products that were recognized by the European Medicines Agency as orphan-designated medicines to treat an orphan disease. An orphan (rare) disease affects a small percentage of the population (about 5 in 10,000 people [21]).

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Table 1 – *continued*

Variable	Definition	Explanation
ATC code[†]	Multiple categories; see below table for all possible values	It was used to classify each product into the corresponding therapeutic area.
Childhood disease	$D = 0$; Not for children $D = 1$; For children	
Health economic evidence		
ICER as a result of the economic analysis performed	$D = 0$; BC analysis demonstrates an ICER below £30,000/QALY and SA an ICER above £30,000/QALY $D = 1$; BC and SA demonstrate an ICER below £30,000/QALY $D = 2$; BC and SA demonstrate an ICER above £30,000/QALY gained $D = 3$; ICER is negative due to negative costs and QALY gain $D = 4$; A cost-minimization analysis is performed	This variable indicated the type of economic analysis performed and backed the submission. CEA and CUA are economic analyses in which the incremental cost per QALY is calculated. The ICER is an outcome of a CEA/CUA. Results of both the base-case economic analysis and the analysis around uncertainty were recorded to analyze the ICER level and whether the ICER exceeded the predefined threshold of £30,000/QALY gained. The SMC does not have a formal ICER threshold; hence, the official NICE threshold was assumed to represent the value upon which a technology is deemed to be cost-effective by the SMC. A cost-minimization analysis assumes similar efficacy and is used to show the difference in cost implications of two or more alternative treatment options. If a range of base-case ICERs was reported because multiple analyses were conducted for different drug comparators, the ICER of an analysis based on an active-controlled trial was preferred to be extracted over the ICER of an analysis based on a placebo-controlled trial. If more than one ICER was reported for the same analysis/comparator as the submission dossier may cover more than one population, we conservatively extracted the higher reported one.
Budget impact at year 5	$D = 0$; Budget impact at year 5 is not mentioned $D = 1$; Estimated net budget impact at year 5 is over £500,000 $D = 2$; Estimated net budget impact at year 5 is below £500,000	The manufacturer is requested to estimate and submit a budgetary impact of introducing a new product into the current treatment setting assuming the product of interest is on the market for 5 y.
Budget impact overestimation/ underestimation	$D = 0$; Not mentioned $D = 1$; Underestimated $D = 2$; Overestimated	This variable indicated whether the SMC stated that the budget impact was overestimated or underestimated. The "not mentioned; no report of the SMC on whether the budget impact was over- or underestimated" was set as the reference case.
Other information		
Company size	$D = 0$; Manufacturer submitting the drug is a small company $D = 1$; Manufacturer submitting the drug is a big company	The manufacturer's company size was defined as big/small, as sorted on the basis of their total revenues. Companies with total revenues of $\geq$1.5 billion[*] were considered as big size companies, whereas firms with total revenues below this cutoff point were considered as small size companies.
Year of submission	2006, 2007, …, 2013	The year when the SMC decision upon recommendation was issued.
Patient interest group presence	$D = 0$; No patient interest group attached comments to submission $D = 1$; A patient interest group attached comments to submission	Patient interest groups are able to collate comments from a number of patients and carers and provide these in the form of a submission of evidence to the SMC as part of the manufacturer's submission.
Resubmission	$D = 0$; Submission for the first time $D = 1$; Submission for at least the second time	This variable indicated whether the submission under analysis is a resubmission. Where there is significant new information about a drug, or new analysis of existing information, the sponsor company may make a resubmission, which is essentially a complete de novo assessment through usual SMC processes. This type of submission is usually after the SMC had already rejected to recommend the product of interest at least once.

Note: $D = 0$ was treated as reference category in logistic regression analyses.

ATC, Anatomical Therapeutic Chemical (ATC) Classification System; BC, base case; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; SA, sensitivity analysis; SMC, Scottish Medicines Consortium.

[*] As sorted and presented in "Fortune Global 500 2009 Pharmaceutical Industry" and "Global 500." CNN. 2008.

[†] ATC codes: A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones and insulins; J, antiinfectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; R, respiratory system; S, sensory organs; V, various.

this potential limitation, a sensitivity analysis was conducted excluding the subset of resubmissions and its impact on the standard error of the parameter estimates was observed.

Results

A total of 463 appraisal documents (full submissions and resubmissions) published on the SMC Web site between January 2006 and July 2013 were reviewed and extracted. Of the 463 submissions, 265 (57%) were accepted for use and 198 (43%) were not recommended for use within NHS Scotland. Of the ones that received a positive opinion, 150 (57%) were accepted for restricted use, for example, for a limited patient population or for a restricted time period, while 115 submissions were accepted for routine use.

Base Case

Table 2 provides an overview of results of univariate analyses including the estimated OR, the probability of positive recommendation, and the number of submissions for each variable and category within a variable. An OR above 1 indicated higher odds of a positive recommendation than rejection. In total, 13 factors demonstrated a significant association with reimbursement recommendation by the SMC (these are marked with an asterisk in Table 2). Of these, 8 factors were related to clinical evidence, indication, and disease characteristics, while 5 factors were associated with economic evidence and size of the manufacturer's company.

Economic evidence seemed to be strongly influential for the reimbursement recommendation. Submissions supported by a cost-minimization analysis had higher odds of receiving a positive recommendation (OR = 8.3; 95% confidence interval [CI] 3.9–17.6) than did submissions supported by a not robust cost-utility analysis (base-case ICER below £30,000/QALY and sensitivity analyses above £30,000/QALY). Similarly, economic evidence showing that the new treatment dominates the comparator treatment (i.e., demonstrating cost savings and yielding additional QALYs) was associated with high odds of a positive recommendation (OR = 6.4; 95% CI 2.2–18.9).

Moreover, it was shown that an active controlled trial (OR = 2.08; 95% CI 1.41–3.07) is preferred over a placebo or an uncontrolled one. A surprising observation was that submissions based on nonsuperior efficacy results against an active comparator, however, had a significant and higher OR than did submissions based on superior efficacy results against an active comparator when compared with uncontrolled trials. This is likely explained, however, by insufficient power.

Variables that demonstrated a statistically significant association with the SMC recommendation in univariate analyses were included in the multivariate regression model and were subject to the variable selection procedure. The backward elimination process resulted in a final multivariate model including seven factors. Four of these were related to health economic evidence, while three were associated with therapeutic indication, disease characteristics, and manufacturer's company size. Results of the multivariate analysis (OR and the *P* values) are presented in Table 3.

Several of the variables that were significant in univariate analyses were eliminated in multivariate analyses because the variance they explained was shared with stronger predictive variables. For instance, an orphan product, which was shown to have a significant impact on the univariate analysis, was not an explanatory variable in the multivariate analysis. The reason is that submissions concerning orphan products demonstrated a high ICER; hence, the ICER is a stronger explanatory variable that eventually remains in the analysis.

The area under the receiver operating characteristic curve of the final multivariate model was estimated to be 0.80, indicating that the prediction accuracy of the developed model was reasonably high; that is, the model was able to predict the SMC decisions correctly in 80% of the cases.

Sensitivity Analysis

The sensitivity analysis, in which applications submitted only once were included in the data set, revealed the same factors to influence the recommendation decision by the SMC. The OR and CIs are similar to the ones from the base case, demonstrating the robustness of the results. Besides, the data set consisted of a small number of resubmissions (115 resubmissions; 25%), which was considered unlikely to introduce any bias in the base-case analysis.

Conclusions

The purpose of the present study was to investigate the weight the different components of evidence, submitted to the SMC for reimbursement, have on the final recommendation decision.

Out of the 463 submissions that were included in the analyses, 265 were accepted for use (57%) and 198 (43%) were not recommended for use within NHS Scotland. Univariate analyses showed that 13 variables significantly affected the SMC decision. Of these 13 variables, 7 variables were shown to have a meaningful impact in the multivariate analysis. Four of these concerned the outcome of the cost-effectiveness analyses; the fact that a submission was supported by a cost-minimization analysis was the strongest positive variable (OR = 10.3) and a submission showing a product not being cost-effective (i.e., an ICER above £30,000/QALY) was the strongest negative predictor (OR = 0.47). The other variables concerned whether the submission was related to a product indicated for a nervous system disease (OR = 0.41), whether it was indicated for nonchronic use (OR = 1.66), and whether the submission was performed by a big company (OR = 2.83).

Other authors have investigated similar research questions but for other countries. For England and Wales, Dakin et al. [6] found that the most influential factors affecting recommendations were the number of randomized clinical trials, inclusion of cost-utility analysis in submission, the ICER, and whether the product of interest was a lifesaving intervention. Devlin and Parkin [7] also found that the ICER had the most influential impact on NICE decisions. The results by Cerri et al. [10] indicated that the following factors were important: demonstration of statistical superiority, the ICER, the number of pharmaceuticals appraised within the same appraisal, and the appraisal year. Harris et al. [12] found that clinical significance, cost-effectiveness, budget impact, and disease severity were the most influential factors for a positive coverage decision for Australia. In The Netherlands, Cerri et al. [11] found the following factors to significantly affect the reimbursement decision of the Dutch national health authority: active comparator of the pivotal trial, the budget impact, the therapeutic indication, and the target population.

The findings of these studies are difficult to be compared because of differences in reimbursement systems, methodologies applied, and sample of reimbursement cases studied. A common finding in Scotland, England and Wales, and Australia, however, was that the ICER is an important criterion for the reimbursement decision [6,7,10,12], surprisingly not in The Netherlands [11]. Other factors that were of significant impact in our analyses, for example, the size of the company and whether the products are indicated for nonchronic use, were not included and analyzed in the other before-mentioned analyses. The therapeutic indication and disease severity were influential in our analyses for Scotland and in The Netherlands and in Australia [11,12], but not in England and Wales [6,7,10].

Table 2 – Results of univariate logistic regression analyses.

Variable	Reference category	Odds ratio (95% CI)	P	Probability of recommendation (%)	Number of Submissions, n (%)
Clinical evidence					
Type of compound, biological	Type of compound, chemical	1.11 (0.73–1.71)	0.619	52.61	120 (26)
Active comparator*	Placebo arm	2.08 (1.41–3.07)	0.000*	67.53	205 (44)
Uncontrolled		0.81 (0.36–1.80)	0.600	44.75	27 (6)
Nonsuperior efficacy vs. active comparator*	Uncontrolled trial	3.05 (1.29–7.19)	0.011*	75.31	117 (25)
Superior efficacy vs. active comparator		2.08 (0.87–4.99)	0.099	67.53	88 (19)
Superior efficacy vs. placebo		1.27 (0.57–2.84)	0.556	55.95	224 (48)
Nonsuperior efficacy vs. placebo		0.50 (0.08–3.05)	0.452	33.33	7 (2)
Superior safety	Nonsuperior safety	2.05 (0.88–4.79)	0.096	67.21	30 (6)
Inferior safety profile		0.96 (0.64–1.44)	0.850	48.98	151 (33)
Uncontrolled trial		0.25 (0.05–1.26)	0.092	37.50	27 (6)
Type trial's primary end point, surrogate end point	Type trial's primary end point, hard end point	1.42 (0.95–2.13)	0.084	58.68	326 (70)
Indication-related evidence					
Given in combination	Given as monotherapy	0.97 (0.65–1.42)	0.865	49.24	164 (35)
First-line treatment	Other treatment lines	1.17 (0.81–1.70)	0.395	53.92	214 (46)
Product indicated for nonchronic use*	Indicated for chronic use	1.79 (1.21–2.67)	0.003*	64.16	166 (36)
Competition, available treatments = 1	Competition, two or more available treatments	1.18 (0.65–2.14)	0.586	54.13	352 (76)
Competition, no available treatment		0.60 (0.37–1.05)	0.076	37.50	55 (12)
Disease characteristics					
No orphan indication*	Orphan indication	2.15 (1.25–3.70)	0.006*	68.25	398 (86)
Childhood disease	Not indicated for children	1.15 (0.71–1.85)	0.573	53.49	91 (20)
ATC code					
ATC A (alimentary tract and metabolism)	ATC B–V	1.61 (0.85–3.08)	0.145	61.69	46 (10)
ATC B (blood and blood-forming organs)*	ATC A, C–V	4.37 (1.66–11.54)	0.003*	81.38	34 (7)
ATC C (cardiovascular system)*	ATC A, B, D–V	0.41 (0.17–0.99)	0.049*	29.08	22 (5)
ATC D (dermatologicals)	ATC A–C, G–V	1.32 (0.38–4.56)	0.665	56.90	11 (2)
ATC G (genitourinary system and sex hormones)	ATC A–D, H–V	2.10 (0.66–4.56)	0.210	67.74	15 (3)
ATC H (systemic hormonal preparations, excluding sex hormones and insulins)	ATC A–G, J–V	0.49 (0.14–1.76)	0.275	32.89	10 (2)
ATC J (antiinfectives for systemic use)*	ATC A–H, L–V	4.82 (1.99–11.69)	0.001*	82.82	42 (9)
ATC L (antineoplastic and immunomodulating agents)*	ATC A–J, M–V	0.63 (0.42–0.94)	0.022*	38.65	151 (33)
ATC M (musculoskeletal system)	ATC A–L, N–V	1.23 (0.50–3.02)	0.658	55.16	21 (5)
ATC N (nervous system)*	ATC A–M, R–V	0.57 (0.34–0.95)	0.033*	36.31	68 (15)
ATC R (respiratory system)	ATC A–N, S–V	0.58 (0.27–1.51)	0.268	36.71	18 (4)
ATC S (sensory organs)	ATC A–R, V	1.20 (0.39–3.73)	0.751	54.55	13 (3)
ATC V (various)	ATC A–S	0.36 (0.11–1.23)	0.103	26.47	12 (3)
Economic evidence					
Cost-minimization analysis performed*	BC below 30, SA above 30	8.29 (3.91–17.58)	0.000*	89.24	94 (20)
Cost savings and QALY gain*		6.44 (2.19–18.86)	0.001*	86.56	28 (6)
ICER below £30,000 (both BC and SA)*		2.96 (1.64–5.36)	0.000*	74.75	105 (23)
ICER above £30,000 (both BC and SA)		0.57 (0.31–1.09)	0.096	36.31	134 (29)
BI year 5 <£500,000	BI not known	1.46 (0.94–2.26)	0.092	59.32	211 (46)
BI year 5 >£500,000		0.81 (0.49–1.33)	0.404	44.73	116 (25)
BI overestimating	BI no mention overestimation/ underestimation	1.51 (0.91–2.52)	0.110	60.22	83 (18)
BI underestimating		0.79 (0.48–1.30)	0.353	44.14	79 (17)

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Table 2 – *continued*

Variable	Reference category	Odds ratio (95% CI)	P	Probability of recommendation (%)	Number of Submissions, n (%)
Other					
Big company*	Small company	2.04 (1.36–3.05)	0.001*	67.11	325 (70)
Resubmission	Full submission	0.80 (0.52–1.22)	0.295	44.44	115 (25)
Patient interest group presence	No presence	0.84 (0.58–1.21)	0.341	45.65	222 (48)
Year of submission					
2006	2007–2013	0.77 (0.47–1.31)	0.358	43.50	69 (15)
2007	2006, 2008–2013	0.80 (0.47–1.36)	0.403	44.44	63 (14)
2008	2006, 2007, 2009–2013	1.09 (0.64–1.86)	0.742	52.15	66 (14)
2009	2006–2008, 2010–2013	1.41 (0.77–2.57)	0.269	58.51	52 (11)
2010	2006–2009, 2011–2013	1.47 (0.81–2.69)	0.209	59.51	68(15)
2011	2006–2010, 2012, 2013	0.76 (0.45–1.28)	0.299	43.18	61 (13)
2012	2006–2011, 2013	1.01 (0.58–1.74)	0.981	50.25	54 (12)
2013	2006–2012	1.31 (0.73–2.35)	0.366	56.71	30 (6)

ATC, Anatomical Therapeutic Chemical (ATC) Classification System; BC, base case; BI, budget impact; CI, confidence interval; ICER, incremental cost-effectiveness ratio; SA, sensitivity analysis.
* Significant impact has been shown.

Implications for Future Reimbursement Submissions

The results of this study present (at least) three important implications for future reimbursement submissions. First, our analyses suggest that the ICER and the uncertainty around the ICER are significant factors for a successful reimbursement submission in the SMC. Consequently, the pricing of the product (including orphan-designated products) should be carefully considered by the manufacturer on the grounds of the implications that the price may have on the reimbursement recommendations of its product [24].

A cost-minimization analysis assumes similar efficacy and is used to show the difference in cost implications of two or more alternative treatment options [25]. The fact that a performance of cost-minimization analyses was associated with a high probability of positive recommendation suggests that the SMC may prefer a case that can be backed up by a simple pharmacoeconomic analysis, such as a cost-minimization one.

Furthermore, it was shown that the trial design is taken into consideration by the SMC. An active-controlled trial is preferred over the placebo one. Therefore, manufacturers should take this into consideration trying to fulfill the reimbursement requirements along with the marketing authorization needs because this tends to be a hurdle for a product's introduction in the market.

Another interesting insight was drawn from the multivariate analysis, which revealed that an application submitted by one of the big pharmaceutical companies had a higher chance of being accepted for use than did an application submitted by a small company. This is likely explained by the fact that big companies have more experience and fund available for conducting the right trials and for building the economic evidence that is needed for SMC submissions. Hence, appropriate funding for high-quality trials and evidence is a necessary tool along the process of a product's development.

Finally, this research makes the importance or weight of different variables (e.g., clinical, health economic, and burden of illness) on the reimbursement recommendation in Scotland transparent. This is relevant for the understanding of all stakeholders of the Scottish reimbursement process (e.g., SMC, manufacturers, patient interest groups, and clinicians). For manufacturers and lobbying organizations, it could help to further improve their reimbursement submissions and claims regarding their products. Moreover, this transparency can be used, if deemed necessary, for further refinement of the current reimbursement process and criteria. For instance, it is important to mention that patient interest groups have already moved forward into flagging their difficulty in accepting the importance of the ICER to the SMC committee and their concerns about the implications on the access of patients to certain effective medicines [26]. Consequently, SMC is requested to introduce a new, more flexible decision-making

Table 3 – Results of the multivariate logistic regression analysis.

Variable	Odds ratio (95% CI)	P
Economic evidence		
Cost-minimization analysis performed	10.30 (4.61–23.05)	0.000
Cost savings and QALY gain	8.91 (2.84–27.89)	0.000
ICER below £30,000/QALY (both BC and SA)	3.08 (1.64–5.77)	0.000
ICER above £30,000/QALY (both BC and SA)	0.47 (0.24–0.91)	0.024
Indication-related evidence		
Product not indicated for chronic use*	1.66 (1.03–2.68)	0.039
Disease characteristics		
ATC N: Nervous system*	0.41 (0.21–0.79)	0.009
Other		
Big company	2.83 (1.68–4.79)	0.000

ATC, Anatomical Therapeutic Chemical (ATC) Classification System; BC, base case; CI, confidence interval; ICER, incremental cost-effectiveness ratio; SA, sensitivity analysis; QALY, quality-adjusted life-year.
* Examples related to products indicated for nonchronic use: product indicated for treatment of major depressive episodes or for manic episodes associated with bipolar I disorder; Example for ATC N (nervous system) products: product indicated for invasive candidiasis or for topical treatment of moderate scalp psoriasis.

framework for the assessment of end-of-life medicines, orphan medicines, and ultraorphan medicines that is not based on cost-effectiveness outcomes [26]. It will be interesting to observe in a future research the consequences of this new approach (when available and implemented) for the assessment process and acceptance rates for these products.

Limitations

Findings of this study should be interpreted with the following limitations. First, no variables related to the decision process (e.g., policy changes, size of the committee, members, and expertise) were considered in the analyses. Second, the ICER threshold of £30,000/QALY was used in analyses because it is evidently reported in SMC appraisal decisions as an evidence that is taken into consideration. Yet, the SMC does not have a formal ICER threshold; hence, this value, being the official threshold applied by NICE, was assumed to represent the value upon which a technology is deemed to be cost-effective by the SMC. The arbitrarily chosen thresholds for the ICER (e.g., £30,000/QALY gained) and the budget impact (e.g., £500,000 in year 5) could have affected the results. Furthermore, it should be noted that even though the SMC assessment does not go beyond the company's submission, it might estimate its own unofficial ICER to support its decision [14,16]. This analysis, however, was dependent on publicly available information, and it was assumed that the base case published by the SMC is the one on which the final recommendation was based.

Finally, in our study, a *positive recommendation* was defined as a product being accepted for use with or without any restrictions. For this study, we did not pursue to separate the full acceptance for use from an acceptance for restricted use because the total number of submissions per level of recommendation would have been too low to draw robust conclusions. In addition, it is unknown whether it was the manufacturer's strategic decision to request reimbursement recommendation with restrictions, or it was the SMC who came to this conclusion given the submitted evidence. Therefore, it cannot be assumed that a restricted acceptance represents a lesser favorable decision because this may serve, for example, the therapeutic indication of the product of interest. Nonetheless, it is acknowledged that future research could take into account the multinomial nature of the recommendation outcome.

The SMC database that was created for this analysis is assessed to be comprehensive, including information from all different components of submitted evidence. In addition, the sample for this analysis is the biggest that has been created for this type of analysis and it is the only one related to the SMC coverage recommendations. Future research could include a consistent assessment of cases and explanatory variables and methodologies across countries to better understand and explain differences across different health care systems.

To conclude, the present study identified the most influential factors to the reimbursement recommendation by the SMC. It was shown that favorable ICER (i.e., base-case ICER and sensitivity analysis around it below £30,000/QALY gained) is crucial for a successful submission. Both univariate and multivariate analyses showed that this comes in combination with the clinical evidence, the target disease, and the company's size, which also play a significant role in SMC reimbursement decisions. It is interesting to observe that these conclusions are in line with the publicly stated objective of the SMC: "Will the medicine be effective? Are current treatments better? Does the medicine give value for money compared to existing treatments? These are the main questions asked while considering new medicines' approval" [15].

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