

Working Paper:

Factors influencing the outcomes of the AMNOG benefit assessment in Germany

Author:

Prof. Dr. Thomas Hammerschmidt
Professor for Pharmamangement

University of Applied Sciences Rosenheim
Faculty for Applied Health and Social Sciences

Hochschulstraße 1
83022 Rosenheim
Germany

Phone: 08031-8052514

E-Mail: thomas.hammerschmidt@fh-rosenheim.de

Original research:

Factors influencing the outcomes of the AMNOG benefit assessment in Germany

Abstract

Background: Since 2011, pharmaceutical companies have to prove the added benefit of new drugs in Germany. The benefit assessment is in relation to an “appropriate comparator therapy” (ACT) defined by the Federal Joint Committee (FJC). Based on the benefit assessment, a reimbursement price is negotiated. In order to prove added benefit, it is essential to provide evidence on patient-relevant outcomes from direct head-to-head comparisons with the ACT. Indirect treatment comparisons and evidence based on surrogate parameters are usually not sufficient. FJC often splits the indication into different subpopulations.

Objective: The objective was to analyse whether factors beyond the clinical evidence have influence on the benefit assessment of the FJC.

Methods: All benefit assessments between 2011 and 2015 were included in the analysis. The benefit for each drug was calculated by weighting the evidence grade, strength of evidence and size of subpopulations. Drugs were then clustered in high, low or no benefit. Univariate logistic regression was used to identify variables with potential influence ($p < 0.25$). Those variables were included in a multivariate logistic regression model and variables with $p > 0.1$ were excluded in a stepwise approach.

Results: The final multivariate logistic regression identified that following variables increase the chance of getting a higher benefit: pharmacologically innovative drug, drugs in disease areas with high unmet medical need, drugs in oncology or infectious diseases, and drugs for which the FJC can split the assessment into subpopulations.

Conclusions: The analysis identified variables beyond clinical evidence that influence the benefit assessment by the FJC and provided a better understanding of decision making by the FJC.

Key Words: AMNOG, HTA, benefit assessment, pharmaceuticals, Germany

Key points for decision makers:

- Clinical evidence on patient-relevant outcomes from direct head-to-head trials is essential for the AMNOG benefit assessment in Germany.
- The study points out that other factors can improve the chance for a good benefit assessment: pharmacologically innovative drug, drugs in disease areas with high unmet medical need, drugs in oncology or infectious diseases, drugs for which the FJC can split the assessment into subpopulations.

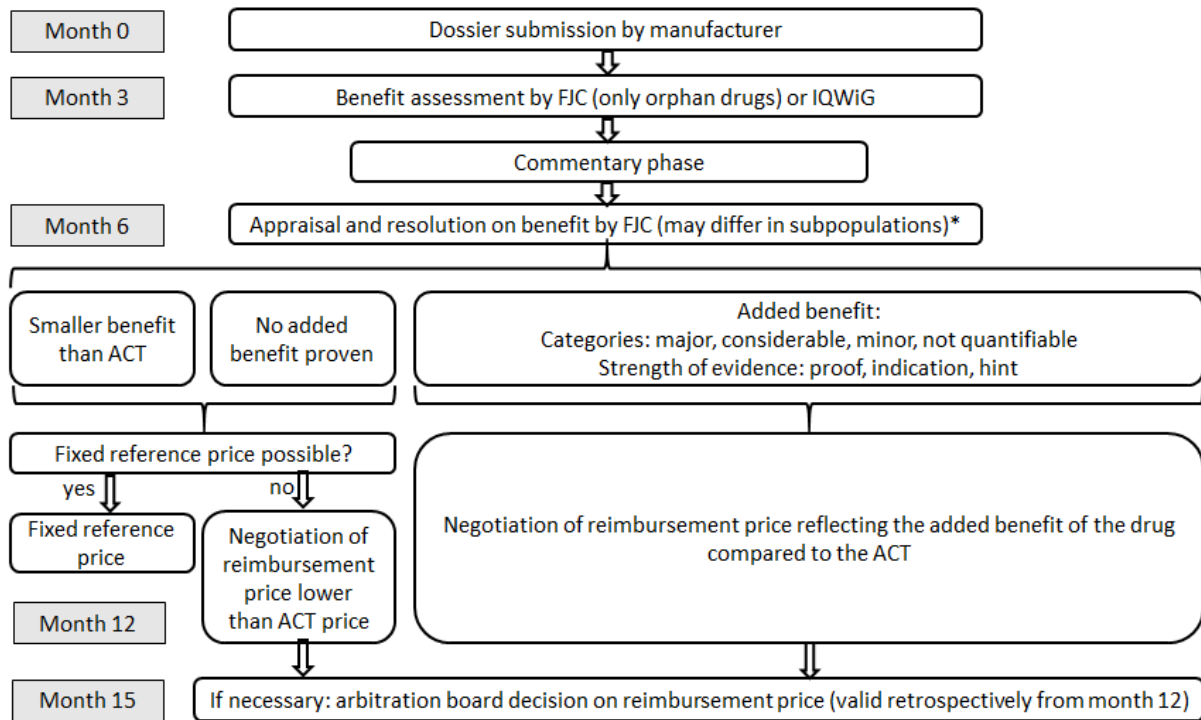
1. Background

In the past, drug prices of new, patent-protected drugs in Germany were not regulated, i.e. free pricing with full reimbursement. Thus, drug prices had been among the highest in Europe [1,2]. In 2011, the German act on the reform of the market for medicinal products (Arzneimittelmarktneuordnungsgesetz, AMNOG) introduced a benefit assessment of new drugs followed by negotiations of a maximum reimbursement price. Today, free pricing is limited for the first twelve months after product launch. After one year, pharmaceutical companies have to lower their price to the negotiated level. However, reimbursement is still granted [3]. Thus, AMNOG introduced the concept of value-based pricing into the German pharmaceutical market [4]. It had three objectives. First, the best and most efficacious drugs should be available in Germany. Second, price and prescription of drugs need to be cost-efficient. Finally, AMNOG should provide a framework for balancing incentives for innovation, adequate care for patients and saving jobs in the pharmaceutical industry. AMNOG resulted in a decrease of drug prices to the lower European level [5] and achieved thus one of the objectives. However, a considerable number of drugs have been taken from the market as a consequence of the AMNOG (see below).

Figure 1 shows the process of the AMNOG. The Federal Joint Committee (FJC, Gemeinsamer Bundesausschuss) appraises the added benefit of a new drug based on a manufacturer's dossier, an assessment by the Institute for Quality and Efficiency in Health Care (IQWiG) and comments on the assessment report made by pharmaceutical companies and experts' opinions in a commentary phase. The benefit is appraised in comparison to a so-called "appropriate comparator therapy" (ACT). The ACT is defined by the FJC and should reflect evidence-based standard of care. In general, only clinical evidence of a new drug in comparison with the ACT serves as a basis for the benefit assessment. If a direct, head-to-head clinical trial is missing, indirect treatment comparisons (ITC) can be considered. However, the chance that ITC will be accepted is very small. In most cases in which ITC have been conducted either the applied methodology was not sufficient or clinical trials included in the ITC were too heterogeneous with respect to study duration or patient population, for instance [6,7]. Furthermore, the added benefit has to reflect a patient-relevant effect, i.e. mortality, morbidity, or quality of life. Surrogate parameters like lab parameters, e.g. HbA1c in diabetes, or radiographic diagnostics, e.g. progression-free survival in cancer, are usually not accepted to prove an added benefit. Only some exceptions are made, e.g. sustained virological response in hepatitis C [8]. Even patient preferences or treatment satisfaction are not accepted as surrogates for quality of life [9]. The outcome of FJC's benefit assessment can be a "smaller" benefit than the ACT or "no" added benefit. In this case, the negotiated price may not lead to higher costs for sickness funds than the ACT. If an added benefit is granted, the FJC classifies the benefit as "minor", "considerable" or "major"; in cases in which it is not possible to quantify the added benefit due to limitations in the clinical evidence, the FJC can classify it as "not quantifiable". Furthermore, the FJC states the strength of evidence for the added benefit with categories of "proof", e.g. two or more clinical trials showing an added benefit, "indication", e.g. only one clinical trial available" or "hint", e.g. one clinical trial with deficits, for instance in study length or with biases. Finally, the FJC can assign different benefit levels in different subpopulations of the therapeutic indication of the drug. Usually, the FJC distinguishes different lines

of treatment or severity of disease. For drug with an added benefit, sickness funds and manufacturer negotiate a price which reflects the benefit, but also takes into account European price levels and the price level within the therapeutic indication.

Figure 1: AMNOG process



IQWiG: Institute for Quality and Efficiency in Health Care; FJC: Federal Joint Committee; ACT: appropriate comparator therapy

*: Orphan Drugs have an added benefit by law until annual sales rise above 50m €

For orphan drugs, the dossier assessment is performed by the FJC office. Orphan drugs have an added benefit as long as their annual sales stay below 50 mio. € [3]. Drugs which can be included in an internal fixed reference price (FRP) group are assessed within the FRP group according to slightly different criteria. If those drugs cannot show a therapeutic benefit, they will be included in the FRP group without a price negotiation.

Usually, direct clinical evidence in comparison to the ACT showing improvements in patient-relevant endpoints is needed to prove an added benefit. Schwander et al. showed that the added benefit is significantly correlated with the “evaluation of pharmaceutical innovations” (EVITA) score which comprises an assessment of efficacy and safety of the drug [10]. Fischer and Stargardt analyzed the impact of the characteristics of the benefit assessment process, evidence generation methods and type of evidence as well as budget impact on the benefit assessment. Process characteristics were not associated with benefit assessment, but the type of evidence was associated for morbidity and adverse events [11]. However, those analyses focused only on a

single variable or univariate analysis and were based on a relatively low number of benefit assessment. The objective of this paper is to analyze factors influencing the German benefit assessments beside the clinical evidence in multivariate approach.

2. Methodology

2.1 Database

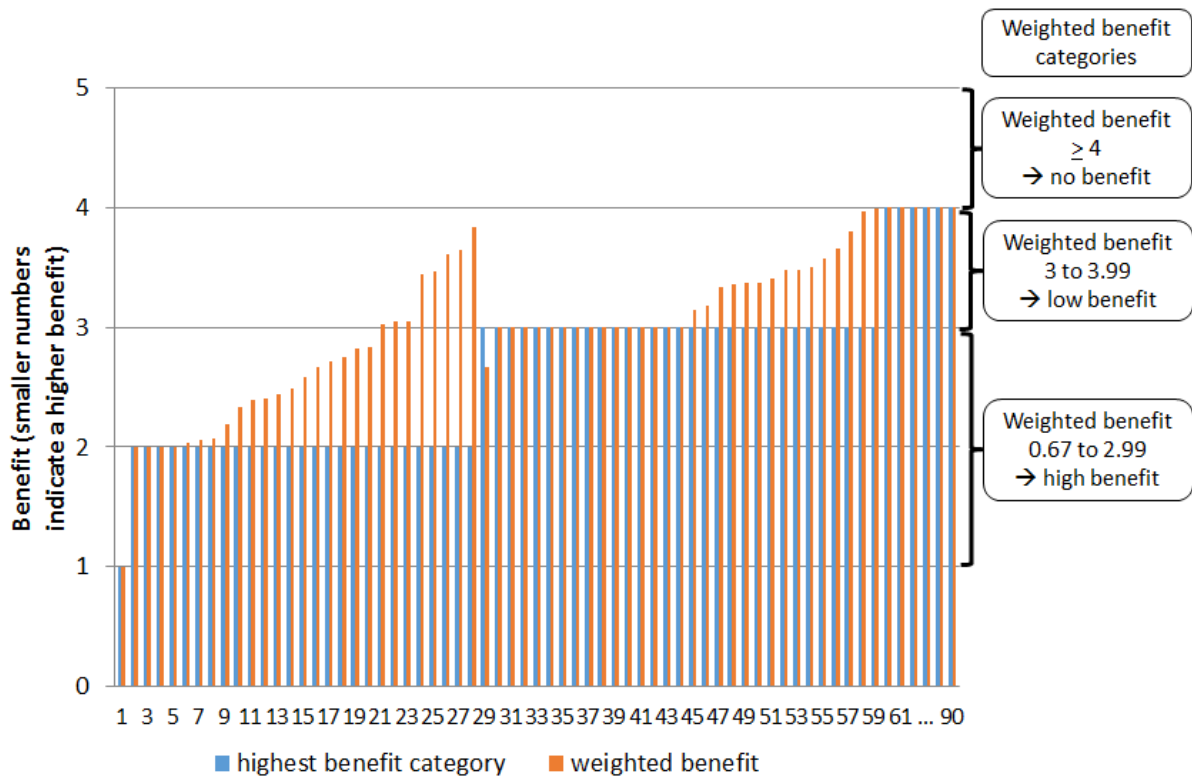
All benefit resolutions made between 2011 and 2015 by the FJC were included in the analysis. Some drugs have been re-assessed in this time-period. The current study focused on the most recent assessment. Drugs with a “not quantifiable” benefit were excluded, because they cannot be assigned to the benefit categories. Furthermore, drugs which have been included in a FRP group were not considered, because the assessment procedure is different.

The documentation of the benefit assessment was the main source for the analysis. It is standardized and contains the manufacturer’s dossier, the dossier assessment by IQWiG or FJC, the resolution of the FJC including its rationale, and the documentation of the commentary phase [12].

2.2 Calculation of benefit

For many drugs, the added benefit differs between subpopulations. In earlier analyses, the highest benefit assigned in one of the subpopulations has been used as a proxy for the added benefit of the drug without considering the strength of evidence or lower benefit levels in other subpopulations [10]. In order to capture the benefit in all subpopulations the following algorithm was applied to calculate an overall benefit of the drug. First, the benefit was graded with 1 for “major”, 2 for “considerable”, 3 for “minor”, 4 for “no” and 5 for “smaller” benefit in each subpopulation. This grade was upgraded by -0.33 for a proof of benefit and downgraded by 0.33 for a hint. Second, a weighted average over all subpopulations was calculated by weighting with the population sizes. For example, fidaxomicin in *Clostridium difficile* infections has a proof of considerable benefit in 19.800 patients (grade 1.67), and no benefit in 13.500 patients (grade 4.00) resulting in an overall weighted benefit of 3.1. This example illustrates that focusing only on the highest benefit granted leads to a considerable benefit. On the other hand, considering all subpopulation leads to a minor overall benefit and reflects the benefit of the drug more accurately. Figure 2 compares the two concepts showing that many drugs with a high benefit in one subpopulation have only minor overall benefit in the whole patient population. In order to analyze influencing factor by multinomial logistic regression analysis, the drugs were clustered in categories of high benefit (weighted average benefit between 0.67 and 2.99), low benefit (3.00 to 3.99) and no benefit (≥ 4.00).

Figure 2: Comparison of highest added benefit and weighted average benefit



2.3 Potential factors influencing the benefit assessment

Table 1 shows the variables which were included in the analysis. Manufacturers complained that the FJC slices the indication to subpopulations in order to deteriorate the overall benefit of the drug. Therefore, it was analyzed whether slicing into subgroups really has an influence on the overall benefit assessment. The experience of the manufacturer might also have an influence on the benefit assessment, because more experienced companies potentially have learned from past assessments. It is unclear whether the choice of generic, older drugs as ACT can result in a better benefit assessment, because it can be assumed that it is easier to prove therapeutic improvement against older therapies than newer innovative therapies. Analyses for other countries have shown that therapy areas can have an impact on the outcome of a health technology assessment which leads to inclusion of the therapy areas into the analysis [13, 14]. Innovativeness was included measured by the so-called Fricke-Klaus classification which classifies drugs as highly innovative, e.g. new mode of action with therapeutic impact, medium level of innovation, e.g. drugs with improved pharmacology, and low level of innovation, e.g. me-too drugs. This classification is mainly based on the pharmacological innovativeness and less on clinical data compared with the EVITA score used by Schwander et al. [10]. The Fricke-Klaus classification was used because the EVITA score assesses mainly the therapeutic benefit and is much more reliant on the clinical data which are also the basis for benefit assessment. EVITA and the AMNOG measure mainly the same concept while Fricke-Klaus focus on pharmacological aspects and can serve as an

indicator for innovativeness which is not necessarily, but potentially correlated with the benefit assessment. Database for the Fricke-Klaus classification was the annually published medical prescription report [15]. Furthermore, medical need for new therapeutic options was assessed based on the severity of disease and number of therapeutic options available. Population size and potential budget impact were included in the analysis to test whether the potential impact on the health care system has an influence on the benefit assessment. The manufacturer's decision to take the drug from the market after the benefit assessment was also analyzed. Finally, the FJC can limit the duration of the benefit assessment and reassess the drug after a period of time. It was analyzed whether this decision influences the benefit assessment of the drug.

Table 1: Definition of variables included in the analysis

Variable	Coding	Definition	Source
benefit	0 = no, 1 = low, 2 = high	benefit weighted by strength of evidence and subpopulations (weighted benefit categories)	[12]
sub pop	0 = no, 1 = yes	FJC appraised benefit in subpopulations	[12]
experience	count	Number of dossiers submitted by manufacturer before recent submission	[12]
ACT price	0 = generic, 1 = mixed, 2 = originator	Price level of therapies defining the appropriate comparator therapy	[12,16]
Therapeutic areas	0 = no, 1 = yes	Drug belongs to specific therapeutic area, i.e. cardiovascular, CNS, dermatology, gastroenterology, hematology, infections, metabolic, musculoskeletal, oncology, ophthalmology, respiratory, urology, others	[12]
innovativeness	0 = low, 1 = medium, 2 = high	Based on pharmacological assessment differentiating drugs with unclear therapeutic value or me-too drugs (0), drugs with improved pharmacology of existing therapeutic principles (1), drugs with an innovative molecule or a new mode of action of therapeutic relevance (so-called Fricke/Klaus classification)	[15]
Medical need	0 = low, 1 = high	Drugs with no or limited therapeutic alternatives and diseases with high mortality or disability risk have a high medical need, including all orphan drugs	[12]
population	Count (million)	Size of patient population	[12]
budget impact	Count (billion €)	Potential budget impact if all patients were treated with the drug under assessment	[12]
opt-out	0 = no, 1 = yes	Manufacturer took drug from the market due to AMNOG	[17]
time-limitation	0 = no, 1 = yes	FJC limited the appraisal for a certain period of time after which the manufacturer has to submit a revised dossier	[12]

2.4 Statistical analysis

Descriptive statistics were calculated for any variable in the complete sample and stratified by outcome group (high vs. low vs. no benefit). Pearson correlation was used to get a first impression of this data. Multinomial logistic regression was used to identify variables with potential influence of the benefit assessment. In a first step, univariate regression was run to ascertain the degree of correlation. Based on these regression, a subset of variables with at least moderate significance ($p < 0.25$) was identified and put forward in a multivariate logistic regression. The multivariate model was reduced by stepwise removing variables with significance levels above a threshold of 0.10 yielding the final model. Statistical analysis was performed with IBM SPSS, version 23.

3. Results

3.1. Univariate analysis

Between 2011 and 2015, 127 drugs have been appraised by the FJC. Four drugs have been included in fixed reference groups. 16 drugs have a non-quantifiable benefit. Thus, 107 drugs were included in the analysis. Of those, 48 (44.9%) had no added benefit, 38 (35.5%) a low benefit and 21 (19.6%) a high benefit. Table 2 shows the characteristics of the included drugs for the complete sample as well as the different benefit categories including the p-value for the correlation of the variables with the benefit category. Table 3 shows the results of the univariate logistic regression.

Some variables were based on the resolutions by the FJC. For 63% of drugs, the FJC sliced the population into different sub-population, ranging from 50% in drugs with no benefit and 81% in drugs with high benefit. The price level of the appropriate comparator therapy was available for 94 drugs and it was a generics' price level for 31.9%, a mixed level for 50.0% and the level of patented-drugs in 18.1% of drugs. The analysis showed a correlation between ACT price and benefit category. The univariate regression revealed a higher chance to achieve a high benefit for drugs with more expensive ACT. Thus, manufacturers more often failed to show an added benefit vs. older off-patent drugs. This can be explained by the fact that clinical studies often target on comparisons with newer patent-protected drugs, e.g. drugs from the same drug class like new gliptins in diabetes which have been compared with other gliptins and not with metformin or sulfonyl urea which were defined as ACT therapies. The FJC limited the duration of their assessment in 17% of their resolutions, but only in 6% of drugs with no benefit and in 32% of drugs with low benefit. Time-limitation of the FJC resolution was significantly more likely in those with low benefit. Manufacturers were significantly less likely to opt-out when the FJC assigns a high benefit.

Other variables were related to the drug itself. For 94 drugs, the degree of pharmaceutical innovation was available. 36.2% had a high degree of innovation e.g. new mode of action, 21.3% a medium degree and 42.6% a low degree of innovation e.g. me-too products. The descriptive analysis showed a clear correlation between level of pharmacological innovativeness and patient-relevant added benefit which showed statistical significance in the univariate regression. Medical need was also highly correlated with the benefit category ranging from 13% of drugs targeting high medical need in the no benefit category to 81% in the high benefit category resulting in a clearly significant increased chance to achieve a higher benefit when targeting higher medical need. With respect to therapeutic areas, oncology drugs represented 24.3% of all drugs assessed followed by 18.7% in metabolic diseases (thereof 80% in diabetes which is the single most assessed indication), 12.1% in infectious diseases, an 11.2% in CNS. All other therapeutic areas accounted for less than 5% of assessments. Oncology drugs represented 8% of drugs without added benefit, but 48% of drugs with a high benefit resulting in a significant positive association of oncology and higher benefit level. The same positive correlation was found for infectious disease drugs. Most CNS and metabolic drugs had no added benefit and were merely unable to achieve a high added benefit level. For all other therapeutic areas, no clear correlation

was found. Furthermore, there was clear negative correlation between the size of the target patient population and the benefit level with an average of 763.000 patients in the no benefit category and 35.000 patients in the high benefit category. The potential budget impact showed no correlation with the benefit assessments. Manufacturers had average experience of 1.5 dossiers before the most recent assessment (range 0-8) which did not differ between benefit categories and is not statistically significant in the regression.

Table 2: Characteristics of included drugs

Variable	Total (n=107) Mean (95% CI)	No benefit (n=48) Mean (95% CI)	Low benefit (n=38) Mean (95% CI)	High benefit (n=21) Mean (95% CI)	P-value
sub pop	0.63 (0.53;0.72)	0.50 (0.35;0.65)	0.68 (0.53;0.84)	0.81 (0.62;0.99)	0.009
experience	1.51 (1.17;1.86)	1.44 (0.89;1.99)	1.71 (1.12;2.30)	1.33 (0.58;2.09)	0.993
ACT price*	0.86 (0.72;1.00)	0.77 (0.56;0.98)	0.85 (0.59;1.11)	1.11 (0.79;1.42)	0.091
cardiovascular	0.05 (0.01;0.09)	0.02 (-0.02;0.06)	0.08 (-0.01;0.17)	0.05 (-0.05;0.15)	0.453
CNS	0.11 (0.05;0.17)	0.21 (0.09;0.33)	0.05 (-0.02;0.13)	-	0.005
dermatology	0.03 (0.00;0.06)	0.04 (-0.02;0.10)	0.03 (-0.03;0.08)	-	0.344
gastroenterology	0.03 (0.00;0.06)	0.04 (-0.02;0.10)	0.03 (-0.03;0.08)	-	0.344
hematology	0.02 (-0.01;0.04)	0.04 (-0.02;0.10)	-	-	-
infections	0.12 (0.06;0.18)	0.04 (-0.02;0.10)	0.13 (0.02;0.24)	0.29 (0.08;0.50)	0.004
metabolic	0.20 (0.12;0.27)	0.25 (0.12;0.38)	0.21 (0.07;0.35)	0.05 (-0.05;0.15)	0.070
musculoskeletal	0.04 (0.00;0.07)	0.04 (-0.02;0.10)	0.03 (-0.03;0.08)	0.05 (-0.05;0.15)	0.995
oncology	0.24 (0.16;0.33)	0.08 (0.00;0.16)	0.32 (0.16;0.47)	0.48 (0.24;0.71)	0.000
ophthalmology	0.05 (0.01;0.09)	0.08 (0.00;0.16)	-	0.05 (-0.05;0.15)	0.301
respiratory	0.05 (0.01;0.09)	0.04 (-0.02;0.10)	0.08 (-0.01;0.17)	-	0.661
urology	0.02 (-0.0;0.04)	0.02 (-0.02;0.06)	0.03 (-0.03;0.08)	-	0.647
other therapeutic areas	0.06 (0.01;0.10)	0.08 (0.00;0.16)	0.03 (-0.03;0.08)	0.05 (-0.05;0.15)	0.418
Innovativeness**	0.94 (0.75;1.12)	0.57 (0.30;0.84)	1.09 (0.78;1.40)	1.47 (1.18;1.73)	0.000
Medical need	0.40 (0.31;0.50)	0.13 (0.03;0.22)	0.53 (0.36;0.53)	0.81 (0.63;0.99)	0.000
population	0.492 (0.300;0.685)	0.763 (0.392;1.135)	0.402 (0.152;0.652)	0.035 (0.008;0.063)	0.000
budget impact	1.15 (0.81;1.49)	0.97 (0.67;1.30)	1.21 (0.49;1.94)	1.41 (0.42;2.40)	0.677
opt-out	0.21 (0.13;0.28)	0.44 (0.29;0.58)	-	0.05 (-0.05;0.15)	0.000
time-limitation	0.17 (0.10;0.24)	0.06 (-0.01;0.13)	0.32 (0.16;0.47)	0.14 (-0.02;0.31)	0.126

*: data available for n=94 drugs with no benefit (n=48), low benefit (n=27), high benefit (n=19)

** : data available for n=94 drugs with no benefit (n=42), low benefit (n=33), high benefit (n=19)

Table 3: Univariate logistic regression

Variable	Low vs. No benefit		High vs. No benefit	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
sub pop	2.167 (0.892;5.264)	0.088	4.250 (1.246;14.502)	0.021
Experience	1.085 (0.859;1.371)	0.492	0.965 (0.711;1.308)	0.816
ACT price*	mixed vs. generic: 1.6956 (0.588;4.891)	0.328	mixed vs. generic: 3.317 (0.802;13.717)	0.098
	originator vs. generic 1.187 (0.277;5.098)	0.817	originator vs. generic 3.958 (0.758;20.665)	0.103
cardiovascular	4.029 (0.402;40.387)	0.236	2.350 (0.140;39.456)	0.553
CNS	0.389 (0.074;2.047)	0.389	-	-
dermatology	0.622 (0.054;7.126)	0.702	-	-
gastroenterology	0.622 (0.054;7.126)	0.702	-	-
infections	3.485 (0.637;19.070)	0.150	9.200 (1.675;50.517)	0.011
metabolic	0.800 (0.289;2.213)	0.667	0.150 (0.018;1.240)	0.078
musculoskeletal	0.622 (0.054;7.126)	0.702	1.150 (0.099;13.423)	0.911
oncology	5.077 (1.482;17.388)	0.010	10.000 (2.633;37.983)	0.001
ophthalmology	-	-	0.550 (0.058;5.240)	0.603
respiratory	1.971 (0.312;12.443)	0.470	-	-
urology	1.270 (0.077;20.996)	0.867	-	-
other therapeutic areas	0.297 (0.032;2.777)	0.287	0.550 (0.058;5.240)	0.603
Innovativeness**	medium vs. low: 5.091 (1.270;20.401)	0.022	medium vs. low: 56.000 (5.460;574.367)	0.001
	high vs. low: 3.564 (1.222;10.390)	0.020	high vs. low: 28.000 (3.169;247.387)	0.003
Medical need	7.778 (2.677;22.594)	0.000	29.750 (7.448;118.838)	0.000
Population (million)	0.672 (0.393;1.147)	0.145	0.078 (0.000;1.799)	0.078
budget impact (billion€)	1.000 (1.000;1.000)	0.531	1.000 (1.000;1.000)	0.353
opt-out	-	-	0.064 (0.08;0.591)	0.010
time-limitation	6.923 (1.787;26.816)	0.005	2.50 (0.461;13.563)	0.288

*: data available for n=94 drugs with no benefit (n=48), low benefit (n=27), high benefit (n=19)

***: data available for n=94 drugs with no benefit (n=42), low benefit (n=33), high benefit (n=19)

3.2 Multivariate analysis

Table 4 shows the outcome of the multivariate logistic regression. After elimination of variables with no significant impact, five variables remained. The slicing of the target population in different sub-population significantly increased the chance to achieve an added benefit. This reflects that FJC often assigns a benefit only in one subpopulation. Pharmacologically more innovative drugs were significantly more likely to achieve a higher added benefit than me-too drugs. The higher the medical need, the more likely drugs showed an added benefit. Drugs in oncology and infectious diseases, mainly targeting hepatitis C or HIV, had higher odds to show added benefit.

Table 4: Multivariate logistic regression

Variable	Low vs. No benefit		High vs. No benefit	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
sub pop	7.979 (1.729;36.815)	0.008	10.909 (1.513;78.687)	0.018
infections	10.645 (1.100;102.990)	0.041	32.306 (2.005;520.434)	0.014
oncology	9.172 (1,403;59.952)	0.021	26.939 (2.797;259.410)	0.004
Innovativeness*	medium vs. low: 4.262 (0.751;24.176)	0.102	medium vs. low: 28.988 (1.917;438.343)	0.015
	high vs. low: 2.504 (0.573;10.946)		high vs. low: 13,772 (0.965;196,524)	
Medical need	15,373 (2.549;92.719)	0.003	34.744 (3.685;327.567)	0.002
McFadden Pseudo-R ²	0.342			

*: data available for n=94 drugs with no benefit (n=42), low benefit (n=33), high benefit (n=19)

4. Discussion

A positive AMNOG benefit assessment relies on clinical data on patient-relevant endpoints in direct head-to-head comparisons with the relevant appropriate comparator therapy which is defined by the FJC. Aspects of the AMNOG process do not influence the outcome of the benefit assessment as shown by Fischer and Stargardt in univariate analysis [11]. This study represents the first multivariate analysis of factors influencing the outcome of the AMNOG benefit assessment and goes beyond those reflecting the clinical evidence or process attributes. The results suggest that pharmaceuticals with an innovative mode of action targeting high unmet medical need indications are more likely to achieve a better benefit assessment. The finding on pharmacological innovativeness is in line with a finding of a univariate analysis by Schwander et al. for Germany [10], but also for Wales [18]. Medical need has been measured by disease severity, e.g. mortality risk, chronically debilitating conditions, complication risk, and number of alternatives. It is based on similar criteria as in the analysis by Svensson et al. who measured disease severity by shortened lifetime or severe mutilating diseases under current treatments and found a clear influence of disease severity on reimbursement decisions in Sweden [19]. Disease severity was also an influencing factor for reimbursement in Australia [20]. Furthermore, drugs in oncology and infectious diseases have also a better chance for a positive benefit assessment. In the univariate analysis, CNS and metabolic drugs appear to have a lower benefit, but this finding was not significant in the multivariate analysis. Similar findings occurred in most analyses of benefit assessments or reimbursement decisions in other countries [13,14,21,22], but not in all [23]

Slicing of the patient population into smaller subgroups has been attacked by manufacturers as a measure to reduce the strength of evidence, i.e. significant benefits in the whole clinical trial population may not be significant after splitting into subpopulations, and to lower the chance of achieving added benefits. However, the FJC usually distinguished whether the licensed indication of the drug under review or comparator therapy requires slicing, i.e. different indications like melanoma or lung cancer, different line of treatments like first or second line treatment, different disease stages for example in COPD, use as monotherapy or in combination.

Rarely, the FJC distinguished subgroups because of different effectiveness; for pertuzumab in metastatic breast cancer the FJC assigned different benefit levels in patients with or without visceral metastases for instance. The recent analysis shows that drugs in which subpopulations can or have to be separated have a better chance to achieve a positive benefit assessment. Thus, the differentiated assessment by FJC supports manufacturers in the benefit assessment. In contrast to analyses from other countries which identified the burden to the health system, e.g. budget impact or population size, as influencing factors for reimbursement decisions [13,19-23], this variable did not play a role in the German benefit assessment.

This study is the first multivariate analysis on factors which influence decision making in the AMNOG process. In contrast to earlier studies, it was focused on the weighted average benefit and not on the highest benefit granted by the FJC [10]. The recent approach showed that a number of drugs with considerable benefit in one subpopulation have only a minor benefit across all subpopulations. Other analysis looked into each subgroup separately without considering the strengths of evidence which is part of the FJC resolution [11]. It was chosen to calculate the weighted average benefit for each drug, because it captures the evidence across all subpopulations in one single number and thus reflects the overall benefit which is the basis for the price negotiations which do not differentiate prices in subpopulations. By clustering the drugs into three benefit categories, information on the heterogeneity on benefits is lost and the clustering is probably oversimplified. Data extraction was based on published information which might not capture all rationales in the appraisal of the FJC.

5. Conclusion

In 2011, Germany introduced a benefit assessment and price negotiation system for new drugs in order to implement value-based pricing and to reduce expenditure for patent-protected drugs. This system did not change the reimburseability of new drugs in Germany, but introduced a measure to lower drug prices. The system is relatively new compared with health technology assessment in other countries like UK, The Netherlands, France, Australia, Sweden and others. It has been shown that direct head-to-head comparisons with the appropriate comparator therapy defined by the Federal Joint Committee (FJC) showing improvement in patient-relevant outcomes are essential to get a positive benefit assessment which is the basis for better outcomes in the price negotiations. The recent analysis revealed that manufacturers are more likely to achieve a positive benefit assessment if they focus on indications with a high medical need and develop drugs with innovative pharmacological mode of actions. In two therapy areas, it is more likely that to achieve a positive benefit assessment, i.e. oncology and infectious diseases. The FJC was attacked in the past for slicing target populations in subpopulations in order to limit the statistical relevance of the clinical data presented by the manufacturer. The analysis showed that the slicing provides a chance for manufacturers to get their drug assigned an added benefit strengthening their position in the price negotiations.

References

- [1] Department of Health. The Pharmaceutical Price Regulation Scheme – 11th Report to Parliament. <https://www.gov.uk/government/publications/pharmaceutical-price-regulation-scheme-11th-report-to-parliament>. Accessed 10 Jul 2016
- [2] Association of the British Pharmaceutical Industry. Understanding the 2014 Pharmaceutical Price Regulation Scheme. http://www.abpi.org.uk/our-work/policy-parliamentary/Documents/understanding_pprs2014.pdf. Accessed 10 Jul 2016
- [3] German Bundestag. Gesetz zur Neuordnung des Arzneimittelmarkt in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz – AMNOG). Bundesgesetzblatt 2010;Part I No. 67: 2262-77.
- [4] Henschke C, Sundmacher L, Busse R. Structural changes in the German pharmaceutical market: Price setting mechanisms based on the early benefit assessment. *Health Policy* 2013; 109: 263-9.
- [5] Hammerschmidt T. Analysis of German new drug prices after AMNIG in relation to European prices. *Gesundh ökon Qual manag*; doi:10.1055/s-0042-111421
- [6] Moeser G, Ecker C. Indirect Comparisons in early benefit assessment. *Gesundh ökon Qual manag* 2013; 18: 235-43.
- [7] Lebioda A, Gasch D, Dippel F-W, Theobald K, Plantör S. Relevance of indirect comparisons in the Germany early benefit assessment and in comparison to HTA processes in England, France and Scotland. *Health Economics Review* 2014;4:31.
- [8] Ruof J, Schwartz FW, Schulenburg J-M, Dintsios C-M. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. *Eur J Health Econ* 2014;15(6):577-89.
- [9] Lohrberg D, Augustin M, Blome C. The definition and role of quality of life in Germany's early assessment of drug benefit: a qualitative approach. *Qual Life Res* 25; 2016: 447-55.
- [10] Schwander B, Banz K, Kauer K, Walzer S. Evaluation of a possible predictor for Federal Joint Committee decisions on early benefit assessments according to the German act on the reform of the market for medicinal products. *Health Policy* 117; 2014: 334-44
- [11] Fischer KE, Stargardt T. Early Benefit Assessment of Pharmaceuticals in Germany: Manufacturers' Expectations versus the Federal Joint Committee's Decisions. *Med Decis Making* 2014; 34: 1030-47
- [12] Federal Joint Committee. Documentation of benefit assessments. <https://www.g-ba.de/informationen/nutzenbewertung/>. Accessed 5 May 2016
- [13] Charapouko M, Majer IM, Raad J, Broekhuizen S, Postma M, Heeg B. Which factors enhance positive drug reimbursement recommendation in Scotland? A retrospective analysis 2006-2013. *Value in Health* 2015; 18(2):284-91.
- [14] Cerri KH, Knapp M, Fernandez J-L. Untangling the complexity of funding recommendations: a comparative analysis of health technology assessment outcomes in four European countries. *Pharm med* 2015; 29: 341-59.
- [15] Schwabe U, Paffrath D. *Arzneiverordnungsreport [Medical prescription report] 2016*. Heidelberg: Springer; 2016.

- [16] Lauer-Fischer. Lauer-Taxe. <https://www.lauer-fischer.de/LF/Seiten/Verwaltung/Kundencenter/1.aspx>. Accessed 5 May 2016
- [17] Head Association of Sickness Funds. Overview in price negotiations. https://www.gkv-spitzenverband.de/krankenversicherung/arzneimittel/rabatt_verhandlungen_nach_amnog/erstattungsbeitraege_verhandlungen_nach_130b_sgb_v/erstattungsbeitraegeverhandlungen_nach_130b_sgb_v_vl.jsp. Accessed 5 May 2016
- [18] Linley WG, Hughes DA. Reimbursement decisions of the All Wales Medicines Strategy Group: Influence of policy and clinical and economic factors. *Pharmacoeconomics* 2012;30:779-94.
- [19] Svensson M, Nilsson FOL, Arnberg K. Reimbursement decisions for pharmaceuticals in Sweden: the impact of disease severity and cost-effectiveness. *Pharmacoeconomics* 2015;33:1229-36.
- [20] Harris AH, Hill SR, Chin G, Li JJ, Walkom E. The role of value for money in public insurance coverage for drugs in Australia: a retrospective analysis 1994-2004. *Med Decis Making* 2008;29:713-22.
- [21] Cerri KH, Knapp M, Fernandez J-L. Public funding of pharmaceuticals in the Netherlands: investigating the effect of evidence, process and context on CVZ decision-making. *Er J Health Econ* 2014; 15: 681-95.
- [22] Dakin H, Devlin N, Feng Y, Rice N, O'Neill P, Parkin D. The influence of cost-effectiveness and other factors on NICE decisions. *Health Econ* 2015;24:1256-71
- [23] Cerri KH, Knapp M, Fernandez J-L. Decision making by NICE: examining the influence of evidence, process and context. *Health Economics, Policy and Law* 2014; 9: 119-41

Compliance with ethical standards:

The author works as consultant for Amgen, AstraZeneca, GlaxoSmithKline, Pfizer, and ViiV Healthcare received fees as speaker for the Bavarian Chamber of Pharmacists and the Association of Research-Based Pharmaceutical Companies (vfa).