IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

El equilibrio entre regulación-innovación en la fijación de precios y financiación de medicamentos

OR

The AMNOG Law

Andreas Gerber-Grote

Encuentro: Los sistemas sanitarios de Alemania y de España

The AMNOG Law

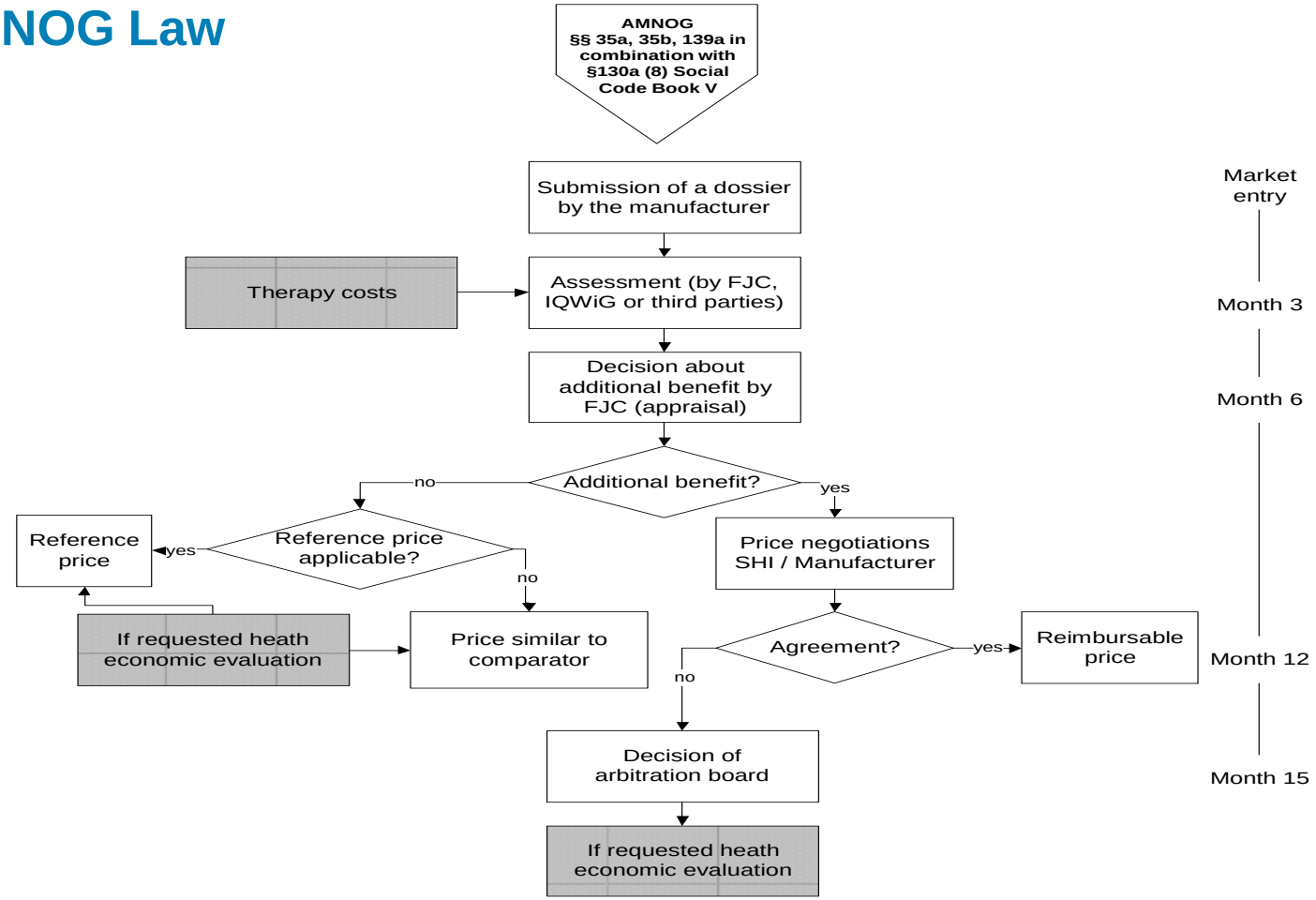


Figure 1: Timeline of the dossier assessment

Legend: Figure 1 illustrates the timeline of the dossier assessment according to the new bill in effect January 1st, 2011. Boxes shaded display where and how IQWiG comes in with regard to health economic criteria in the decision making process on drug prices in Germany.

Extent of added benefit: six categories, legal basis

major added benefit

considerable added benefit

minor added benefit

added benefit proven, but not quantifiable

no added benefit has been proven

less benefit than that of the appropriate comparator

Criteria in accordance with AM-NutzenV*

sustained and great improvement ^ (cure, major increase in survival time, long-term freedom from serious symptoms, extensive avoidance of serious side effects)

marked improvement ^ (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant avoidance of serious adverse effects, important avoidance of other adverse effects)

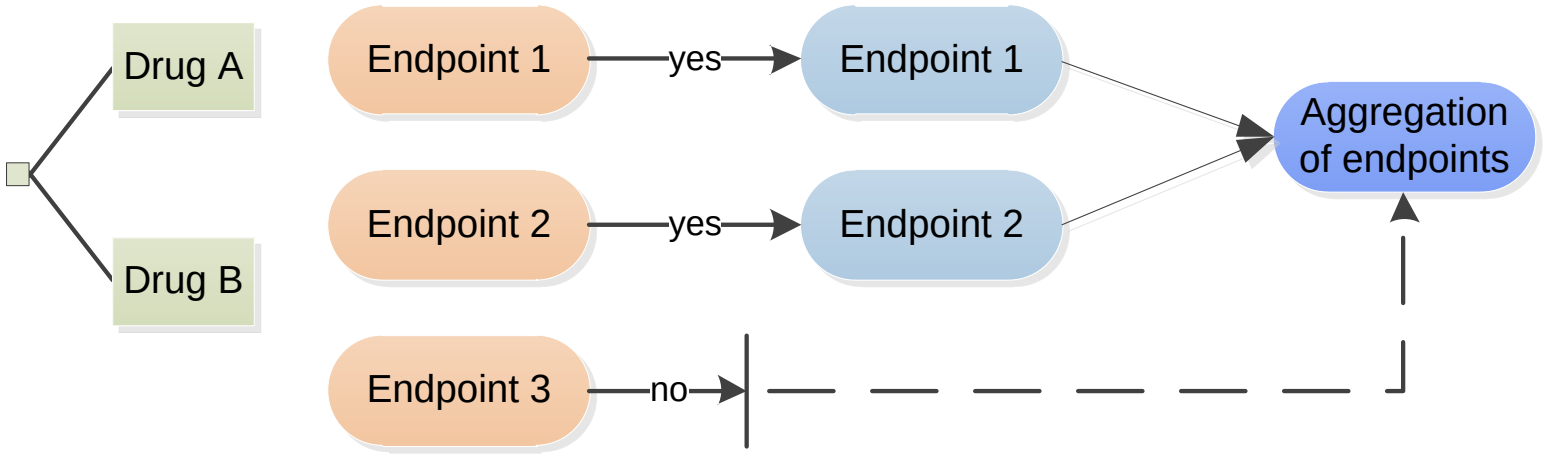
moderate and not only marginal improvement ^ (reduction in non-serious symptoms, relevant avoidance of side effects)

*Regulation for Early Benefit Assessment of New Pharmaceuticals

^in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

Process of assessing "added benefit"

Step 1	Step 2	Step 3	Step 4
Choice of appropriate comparator (G-BA)	More or less benefit? More or less harm? Yes / no decision	Extent of added benefit /harm (categories based on quality of endpoint and effect size)	Aggregated statement on added benefit (considers benefits and harms)



Added Benefit Criteria (developed by IQWiG on the basis of requirements laid out in §35a Social Code Book)

		Outcome Category			
		Survival Time (Mortality)	**Symptoms (Morbidity)**	***Quality of Life***	**Adverse Effects**
Added Benefit	**Major** **sustained great improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator	Major increase in survival time	Long-term freedom from serious (*or severe*) symptoms (*or late complications*)	*Major improvement in quality of life*	Extensive avoidance of serious (*or severe*) adverse effects
	Considerable **marked improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator	Moderate increase in survival time	Alleviation of serious (*or severe*) symptoms (*or late complications*) *Significant reduction in non-serious (or non-severe) symptoms (or late complications)*	*Significant improvement in quality of life*	Relevant avoidance of serious *(or severe)* adverse effects Significant avoidance of other (*non-serious or non-severe*) adverse effects
	Minor **moderate and not only marginal improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator	*Any increase in survival time*	*Any reduction in serious (or severe) symptoms (or late complications)* Reduction in non-serious *(or non-severe)* symptoms *(or late complications)*	*Relevant improvement in quality of life*	*Any reduction in serious (or severe) adverse effects* Relevant avoidance of *(other, non-serious or non-severe)* adverse effects
italics: AM-NutzenV.					

Sources: AMMOG (Pharmaceutical Market Restructing Act), AM-NutzenV (companion regulation), IQWiG General Methods Version 4 (2011)

Added Benefit – Translation into Statistical Measures

		Outcome Category			
		Survival Time (Mortality)	**Serious *(or Severe)*** Symptoms *(or Late Complications)* and Adverse Effects	***Quality of Life***	**Non-Serious *(or Non-Severe)*** Symptoms *(or Late complications)* and Adverse Effects
Added Benefit	**Major** **sustained and great improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator	Major increase in survival time **CI_S: 0.85** (RR_1 = 0.50)	Long-term freedom or extensive avoidance **CI_S: 0.75** (RR_1 = 0.17) **and risk ≥ 5%** [2]	*Major improvement* [1] **CI_S: 0.75** (RR_1 = 0,17) **and risk ≥ 5%** [2]	Not applicable
	Considerable **marked improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator	Moderate increase in survival time **CI_S: 0.95** (RR_1 = 0.83)	Alleviation or relevant avoidance **CI_S: 0.90** (RR_1 = 0.67)	*Significant improvement*[1] **CI_S: 0.90** (RR_1 = 0.67)	Significant avoidance **CI_S: 0.80** (RR_1 = 0.33)
	Minor **moderate and not only marginal improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator	*Any (statistically significant) increase in survival time* **CI_S: 1.00**	*Any (statistically significant) reduction* **CI_S: 1.00**	*Relevant improvement*[1] **CI_S: 1.00**	Relevant avoidance **CI_S: 0.90** (RR_1 = 0.67)

Source: IQWiG

Example Ticagrelor

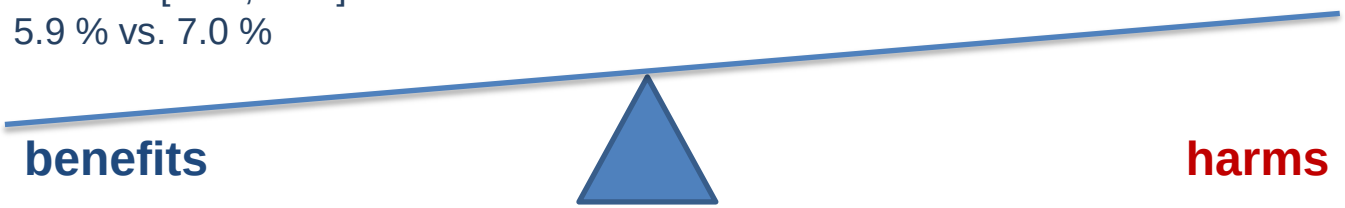
1. Overall survival: proof of considerable added benefit (marked improvement)
   HR 0.73 [0.60; 0.89]
   3.8 % vs. 5.3 %

2. Cardiovascular survival: proof of considerable added benefit
   HR 0.70 [0.56; 0.87]
   3.1 % vs. 4.6 %

3. Morbidity (myocardial infarction): implication of considerable added benefit
   HR 0.85 [0.72; 1.00]
   5.9 % vs. 7.0 %

Adverse events (dyspnoea): proof of greater harm of a considerable extent
RR 0.55 [0.49; 0.62]
14,0 % vs. 7,7 %

Discontinuations due to AEs: proof of greater harm of a minor extent
RR 0.70 [0.60; 0.81]
8.2 % vs. 5.7 %



- Proof of an overall considerable added benefit of ticagrelor versus comparator demonstrated for people with unstable angina/NSTEMI

Examples: Benefit Assessment Results for Advanced-Stage Cancer Treatment Innovations

Considerable added benefit: Zelboraf® (Vemurafenib)

Indicated for treatment of unresectable or metastatic melanoma with BRAF-V600E mutation

Patient group	Endpoint with stat. sig. effect	Probability of benefit or harm	Extent of benefit or harm	Overall conclusion
Patients unresectable or metastatic melanoma with BRAF-V600E mutation	Overall survival	Indication	Major ↑	Indication of considerable added benefit
	Overall rate of severe adverse events (CTCAE Grade ≥ 3)	Indication	Major ↑	
	Overall rate of serious adverse events	Indication	Major ↑	

Source: IQWiG

Benefit varies per patient group: Jevtana® (Cabazitaxel)

Indicated for treatment of metastatic hormone-refractory prostate cancer (mHRPC) in patients previously treated with a docetaxel-containing treatment regimen

Patient group	Endpoint with stat. sig. effect	Probability of benefit or harm	Extent of benefit or harm	Overall conclusion
Patients who are not eligible for further treatment with docetaxel ("best supportive care population")	Overall survival	≥ 65 years: Indication	Major ↑	For patients ≥ 65 years: Indication of a considerable added benefit
		< 65 years: Hint	Not quantifiable ↑	
	Overall rate of adverse events of the CTCAE Grade ≥ 3	Indication	Considerable ↑	For patients < 65 years: Hint of an added benefit (extent "not quantifiable", at most, "considerable")
	Overall rate of serious adverse events	Indication	Major ↑	
	Overall rate of discontinuations due to adverse events	Indication	Considerable ↑	
Patients for whom further treatment with docetaxel is still an option ("docetaxel retreatment population")	-	-	-	No added benefit (no data)

Source: IQWiG

Benefit varies with patient endpoint: Yervoy® (Ipilimumab)

Indicated for patients with advanced melanoma who have already been treated

Patient group	Endpoint with stat. sig. effect	Probability of benefit or harm	Extent of benefit or harm	Overall conclusion
Patients with advanced melanoma who have already been treated	Overall survival	Indication	Major ↑	Indication of a considerable added benefit
	Overall rate of immune-related adverse events	Indication	Considerable ↑	
	Study discontinued due to immune-related adverse events	Indication	Considerable ↑	
	Severe immune-related adverse events(≥ CTCAE Grade 3)	Indication	Major ↑	
	Serious immune-related adverse events	Indication	Major ↑	

Source: IQWiG

No quantifiable added benefit: Halaven® (Eribulin)

Indicated for treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease

Patient group	Endpoint with stat. sig. effect	Probability of benefit or harm	Extent of benefit or harm	Overall conclusion
Patients for whom treatment with taxanes or anthracyclines is no longer an option	Overall survival	Hint	Not quantifiable, at best considerable ↑	No added benefit proven
Patients, in whom further treatment with taxanes or anthracyclines is still possible	-	-	-	No added benefit proven

Source: IQWiG

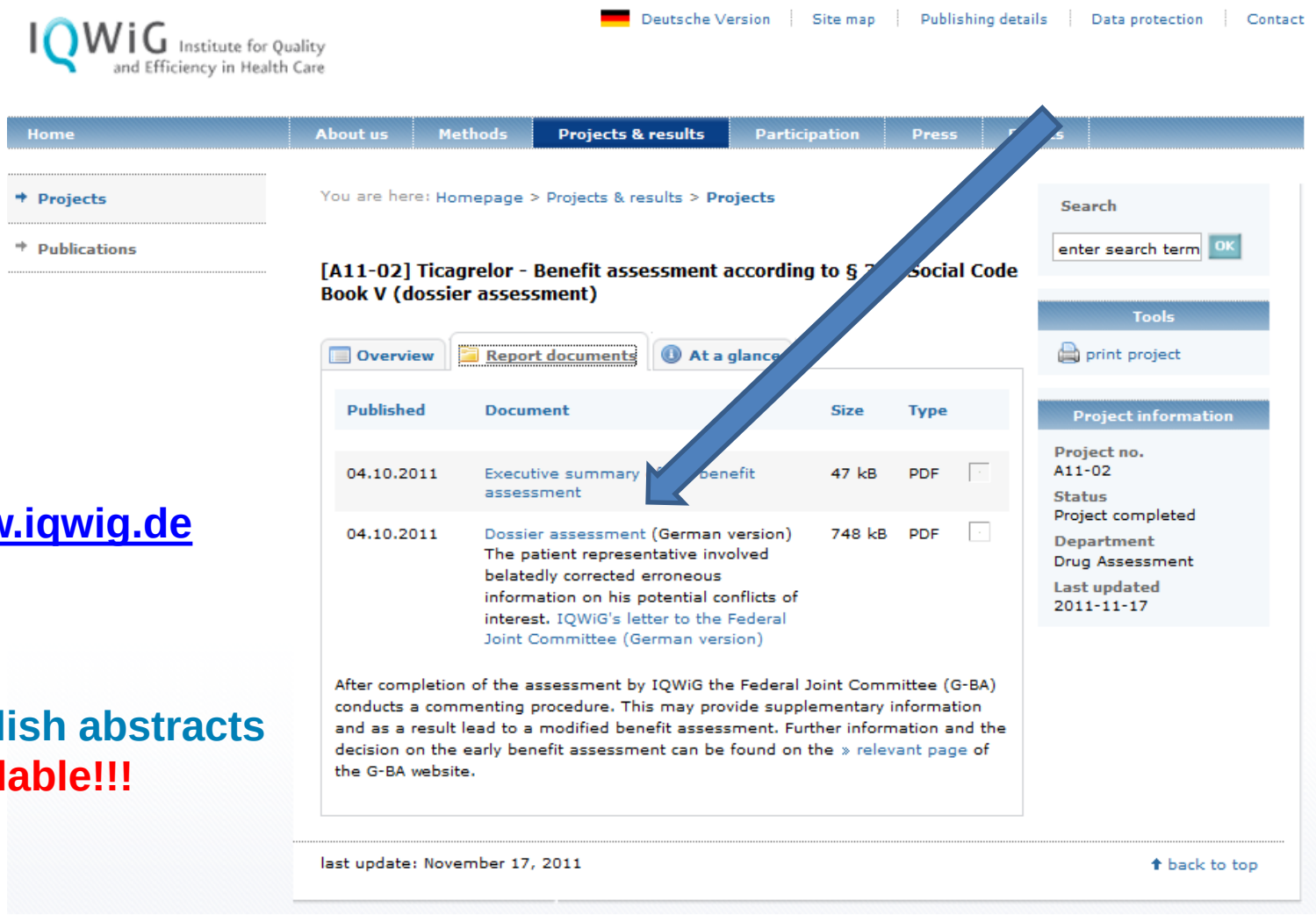
No added benefit: Caprelsa® (Vandetanib)

Indicated for treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease

Patient group	Endpoint with stat. sig. effect	Probability of benefit or harm	Extent of benefit or harm	Overall conclusion
Patients with unresectable locally advanced or metastatic symptomatic or progressive medullary thyroid cancer	-	-	-	No added benefit (no data)

Source: IQWiG

How to retrieve IQWiG reports



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English abstracts available!!!

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ticagrelor –

Benefit assessment according to § 35a Social Code Book V[1]

Extract

How to retrieve the manufacturers' dossiers

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

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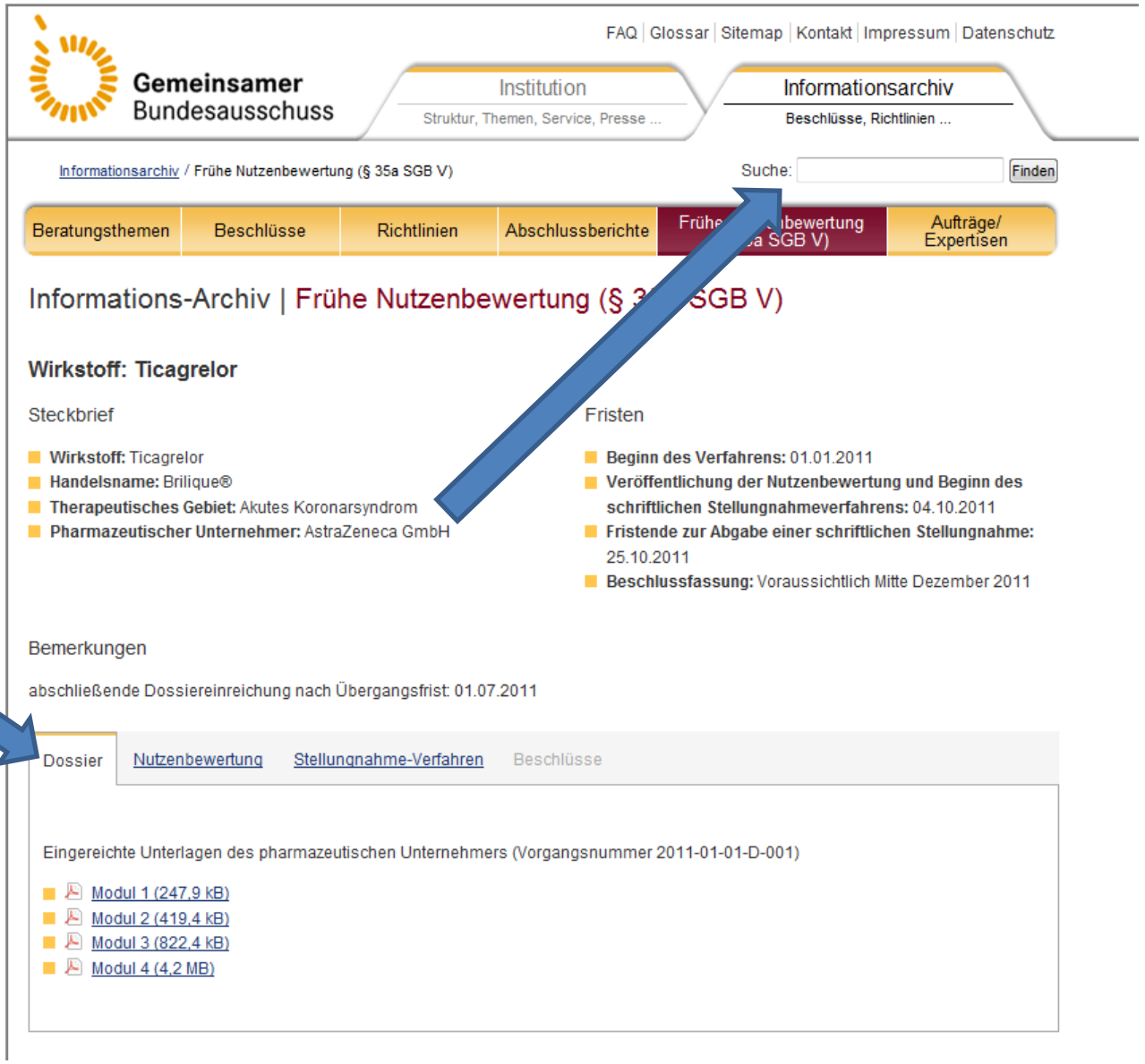
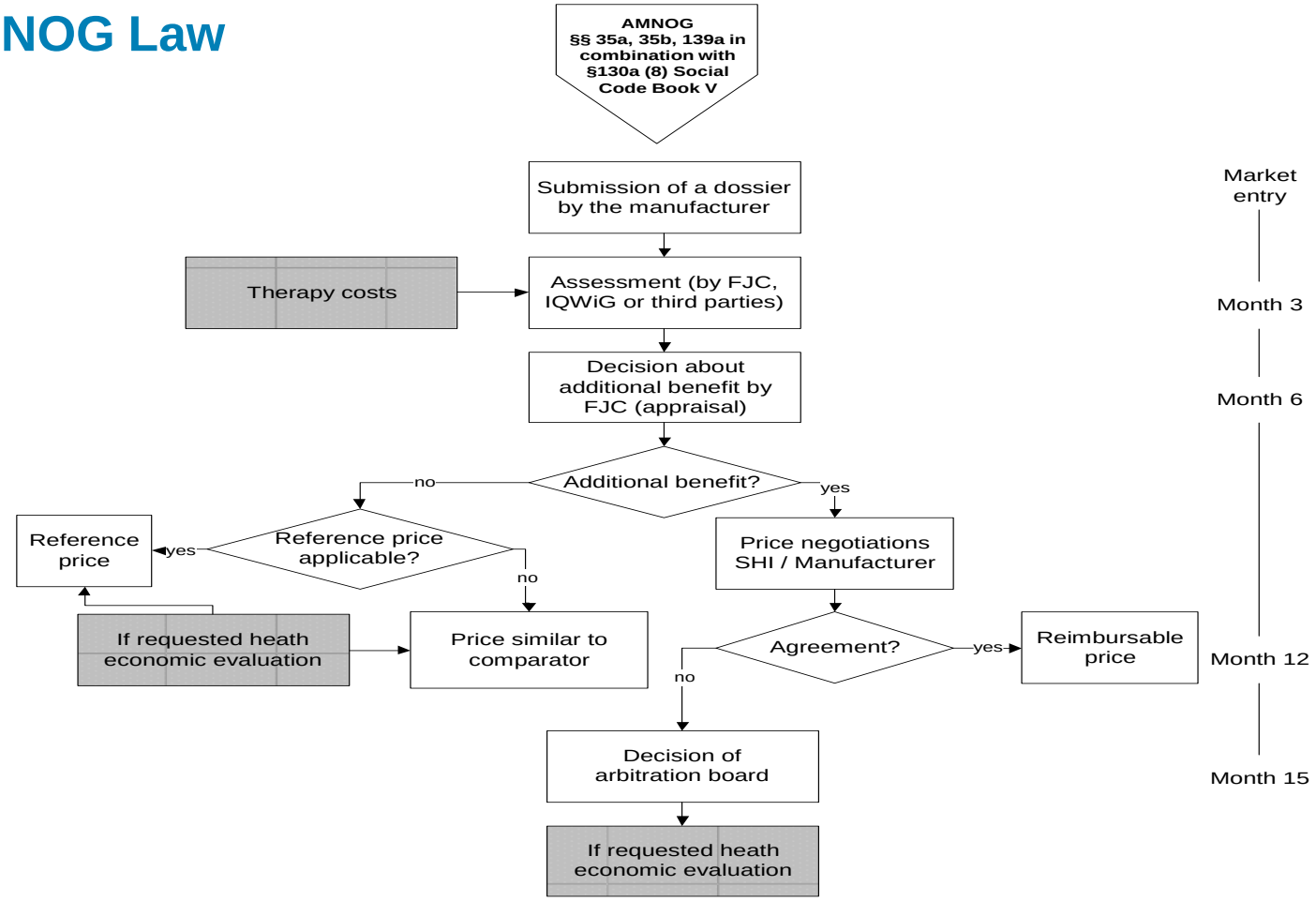
Only German versions available



The AMNOG Law



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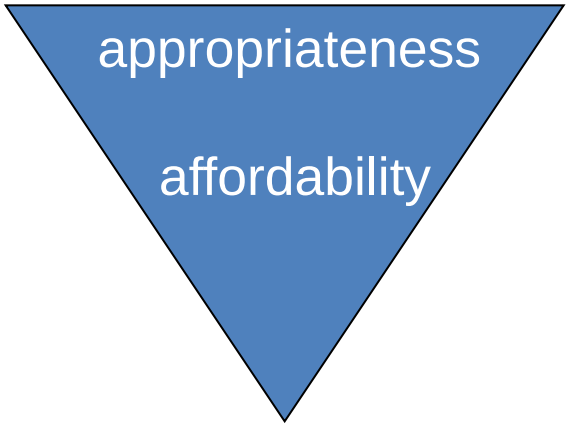
What is the question for health economics to answer in the German system?

SHI as constituency of insurees paying contributions

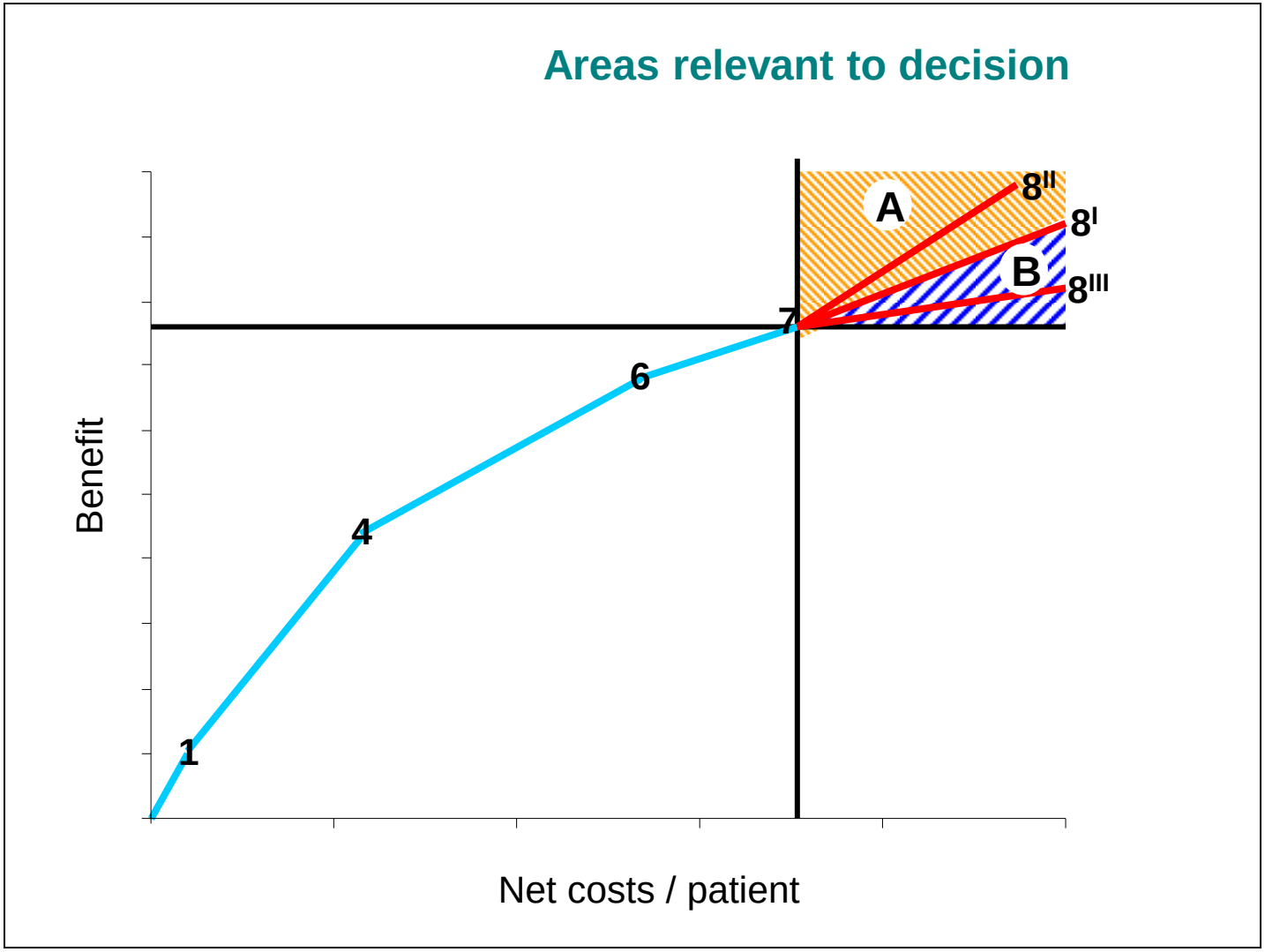


Pharmaceutical manufacturer(s)

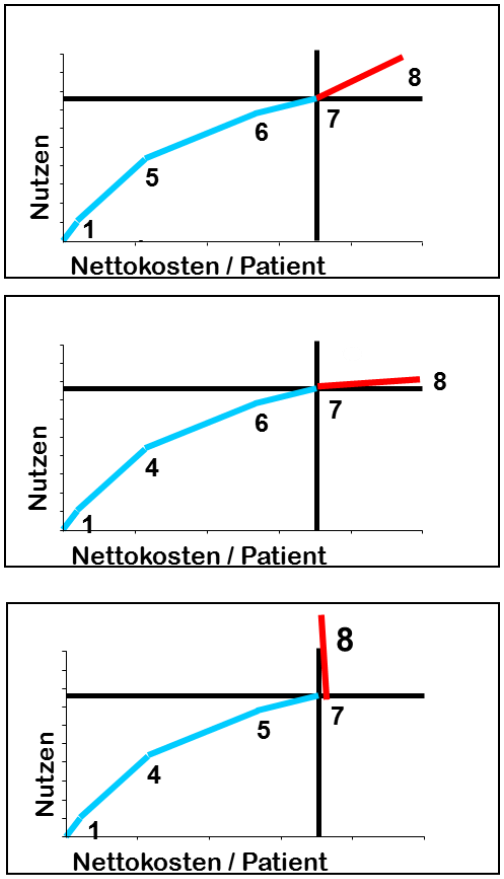
Persons that are in need of a specific therapy/ drug (legal entitlement)

Objective: To inform price negotiations between SHI funds and manufacturers

Efficiency Frontier



Rationale: Why weighting?



- Plot efficiency frontier for various patient-relevant outcomes on the basis of health economic evaluation
- Weighting of endpoint-specific efficiency frontierts to arrive at a reimbursable price
- Patients‘ preferences as a basis for the weighting process as they are experts in their specific disease area
- Elicitation of patients‘ preferences via
  - Analytic Hierarchy Process (AHP)
  - Conjoint Analyse (CA)

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