Registry studies: the key to successful German HTA submissions

The extended application-accompanying data collection (EAD) in the context of the AMNOG process

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A new instrument has been available for German Health Technology Assessments (AMNOG process, Arzneimittelmarktneuordnungsgesetz, Pharmaceuticals Market Reorganization Act) since summer 2019. It is called the "erweiterte anwendungsbegleitende Datenerhebung" (extended application-accompanying data collection, EAD). This instrument was introduced by the new law, GSAV (Gesetz für mehr Sicherheit in der Arzneimittelversorgung, Law for More Safety in the Supply of Pharmaceuticals), and it allows the G-BA (Gemeinsamer Bundesausschuss, Federal Joint Committee) to request the collection of post-launch data accompanying the application of selected drugs.

However, a clear statement was missing with regard to which method would be the best for the EAD. In order to evaluate suitable methods potentially available for the EAD, the G-BA therefore commissioned the IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Independent Institute for Quality and Efficiency in Health Care) to prepare a concept of how to best generate the needed data for the EAD. The key outcome of the corresponding Rapid Report published in January 2020 was that registry studies are the most promising way to collect these data.

After the IQWiG Rapid Report was published, many clients contacted us, and their most frequently asked question was:

How should a registry be built and a registry study designed so that the HTA will be a success?

Therefore, in this white paper, Cerner Enviza's and ZEG-Berlin's registry experts first want to provide answers and an overview of what is needed for successful registry studies and what is most important when a submission in terms of the GSAV is planned in Germany.

In order to provide a full picture, Dr Alexander Wilke – Market Access and AMNOG Expert – provides additional insights regarding the AMNOG process, especially when it comes to GSAV-related submissions.

Contents

1.0. What is the extended application-accompanying data collection?

In June 2019, the "Law for More Safety in the Supply of Pharmaceuticals" (GSAV) was passed by the Bundestag and thus entered into force.

According to the GSAV, the G-BA is authorised to request the collection and evaluation of application-related data for the benefit assessment of orphan drugs, pharmaceuticals with conditional approval and approval granted in exceptional circumstances from pharmaceutical companies.

Following the will of the legislator, studies with evidence levels lower than RCT (i.e. non-randomised data) should be used for the derivation of a (quantifiable) additional benefit for these drugs.

GSAV in the context of the EMA regulations:

Regarding the approval decisions for this group of medicinal products, the EMA confirms a positive benefit-risk ratio when fulfilling an unmet medical need in a situation in which the data required for regular approval can only be provided at a later point in time or the provision thereof is impossible. Based on these approval decisions by the EMA, the German legislator now provides that the new law GSAV take into account non-randomised data to derive a (quantifiable) additional benefit. With the stipulation to also accept evidence with weak outcomes for the benefit assessment (AMNOG), the legislature enables the required congruence between the benefit assessment (AMNOG by G-BA) and the findings of the licensing authority (EMA).

The aim of the extended application-accompanying data collection is as follows:

The regulation of the extended application-accompanying data collection is a massive intervention in the AMNOG process. The G-BA can opt for an "approval under requirements", specifically for orphan drugs, for Advanced Therapy Medicinal Products (ATMPs) or for medications with a special indication area. The G-BA decides on an extended application-accompanying data collection if the current evidence is not valid enough to sustain the scope of an additional patient-related benefit.

This is a completely new process that has a major impact on prescription and reimbursement price negotiation. In addition, the pharmaceutical company obtains no more than a "non-quantifiable additional benefit" as an "interim" outcome of the AMNOG process. (This is a weak starting position for reimbursement price negotiation.)

The overall aim of the extended application-accompanying data collection process is defined as collecting data, based on real-world evidence, to quantify the "non-quantifiable additional benefit" for the final AMNOG decision.

Tip box:

The aim of the data collection is to improve the evidence base.

This means that data collection is only justifiable if it can be expected that this data can generally be used for the quantification of an additional benefit by G-BA.

Pharmaceutical companies should also use this for themselves! No obligation to collect data without a result for the AMNOG process is expected.

It should also be checked whether any data requirements/register requirements that have been requested by the EMA/FDA and that the pharmaceutical company has already implemented are sufficient to quantify the additional benefit. The G-BA is obliged to accept implemented data collections if they are suitable for quantification of an added benefit.

What G-BA means by "healthcare-related data":

It is important not to equate "healthcare-related data" with "real world evidence data". This is one of the most common misinterpretations of the additional data requirements in the AMNOG process. Healthcare-related ("Versorgungsnahe Daten") data for the benefit assessment of medicinal products are defined as follows:

a) Healthcare-related data is collected from the patient populations for which there is an indication for the drug to be assessed as part of the approval.

b) Data must be collected from an indication-specific registry.

c) When data related to healthcare are collected, treatment is carried out without specific requirements.

d) Data from international or European data sources (e.g. registries) must fulfill the criteria a) and b), and they must be transferable and reflect the specific features of the German health system.

The goal of collecting healthcare-related data does not require that data collection be limited to data recorded in everyday care. The IQWIG further clarifies that statement, saying that the collection of data from daily practice is not sufficient.

Such a misinterpreted limitation of data collection would rather jeopardize the aim of the benefit assessment.

For the benefit assessment, data that are not documented in everyday treatment for all patients (e.g. data on health-related quality of life, symptoms or side effects) are regularly required. Health-related data must also be sufficiently valid and structured to enable a benefit assessment.

2.0. Risk matrix — When does the risk for an EAD increase?

In this chapter, we would like to present a tool that can help pharmaceutical companies to assess the potential risk of an EAD. The more companies take these risks into account in their market access AMNOG strategy, the more efficiently personnel and financial resources can be managed, or even further data collections can be planned that improve the overall result of the benefit assessment and thus, of course, also directly correlate with the result of the reimbursement price negotiation.

2.1. Evidence gap:

The main criterion for the G-BA to initiate an extended application-accompanying data collection is the extent of the "evidence gap". The G-BA criteria for clinical studies, their endpoints, statistical methods and comparative therapies used, differ significantly from those of the EMA and the FDA. The German benefit assessment is based on the comparison between the new therapy and an appropriate comparator therapy defined by the G-BA.

Special case orphan drugs:

Orphan drugs have the advantage that they do not have to compare themselves to a comparator therapy in the German AMNOG process either. Based on law, orphan drugs have a "non-quantifiable additional benefit". Nevertheless, the G-BA assesses the extent of the added benefit for orphan drugs in the AMNOG process, and this is where the danger is.

In most cases, orphan drugs and ATMPs cannot fulfill the G-BA's requirements for clinical data and are therefore particularly at risk for expanded data collection.

The "evidence gap" describes the data gap between the data that are available for the product and the data that the G-BA need for a benefit assessment, especially for defining the patient-relevant additional benefit.

Examples:

Endpoints by category	Data available	Evidence gap
Mortality (with acceptable primary endpoint*)	Yes	No
Mortality (with no acceptable primary endpoint)	Yes	Yes
Quality of life	Yes	Could be
HR-quality of life**	No	Yes
Morbidity	No	Yes

* primary endpoint must be accepted by G-BA/IQWIG (e.g. no combination endpoints)

** HR-quality of life = Health-related quality of life (accepted from G-BA)

2.2. Risk matrix:

The risk matrix should help companies to identify the potential risk for an extended application-accompanying data collection process:

Criteria	Product fulfilled the criteria of EAD	Measure and next step
If the additional benefit is unclear (cannot be quantified), GBA can now request an "extended data collection" to clarify the additional benefit:		
a) Products with conditional approval		
b) Products with approval under exceptional circumstances		
c) Orphan drug		
Analysis of evidence GAP:		The more "yes" responses, the higher is the risk for an extended data collection. The risk should now be verified quickly. (e.g. discussions with the GBA etc.)
Mortality		
Morbidity		
Quality of life (HR — quality of life)		
Safety		
Long-term safety/long-term efficacy		
Mode of action		
Limitation from GBA perspective possible based on the rules of procedure of the GBA? (e.g. prescription of the product only through on the EAD participating physicians)		
Other restrictions possible based on the rules of procedure of the GBA? (e.g. prescription of the product only in special centers which fulfill special quality requirements on infrastructure, process or outcome quality		
Based on the Rapid Report of the IQWIG institute, is an "additional data collection" for the product in principle possible?		
From the perspective of the German healthcare system is there a "public interest" for an additional data evaluation? (e.g. genetic therapy, ATMP etc.)		
Is an EAD feasible in all cases (e.g. extended documentation requirement such as an 18-month clinical protocol and outcome analysis or, from a legal point of view, "unreasonable hardness")?		
Is an indication-based registry possible? Is it possible to develop comparative RTCs? Has the registry the needed data for a comparative treatment as well?		
Are there any ongoing or planned other data collections?		

Figure 1 Risk matrix extended application-accompanying data collection (source I.f.G.V.)

The extent and importance of the evidence gap correlating directly with the probability for an extended application-accompanying data collection.

3.0. Requirements for the extended application-accompanying data collection

According to IQWIG and G-BA, the optimal process for passing the extended application-accompanying data collection is via registry studies after building an indication-based registry.
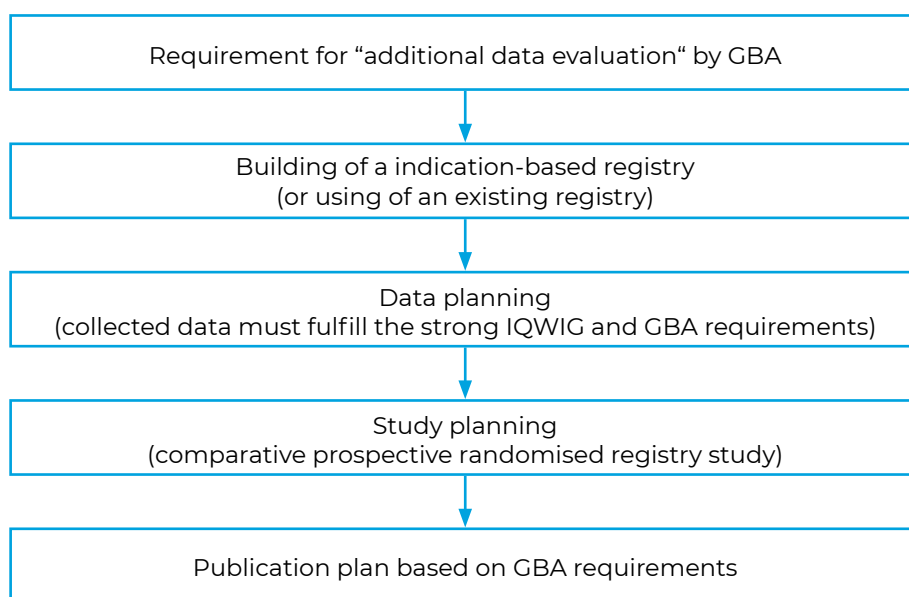
If routine practice data ("Versorgungsnahe Daten") are to be used for the AMNOG benefit assessment, especially for measuring the patient-related benefit based on the rules of procedure of the G-BA, it must be taken into account that the basis of any statement about the effects of interventions is a comparison.

Only on the basis of comparison is it possible to differentiate between "after intervention A" and "because of intervention A", which is necessary for a causal statement.

From these considerations, it follows that single-arm studies or individual study arms are not relevant as outcomes of the extended application-accompanying data collection for a final decision through G-BA on the scope of an additional patient-related benefit for the new product.

Only comparative study designs are relevant for the final decision on the scope of the additional patient-related benefit.

Process pathway:

Requirement for "additional data evaluation" by GBA

↓

Building of a indication-based registry
(or using of an existing registry)

↓

Data planning
(collected data must fulfill the strong IQWIG and GBA requirements)

↓

Study planning
(comparative prospective randomised registry study)

↓

Publication plan based on GBA requirements

Study designs and methods for collecting health-related data (independent of clinical question)		

Study designs for additional data collection

Comparison without randomisation	Comparison with randomisation
Parallel control (not randomised comparison as part of a study)	Comparison of different single arms of multi- or single-arm studies studies	Randomised controlled study	Adjusted indirect comparison via bridge comparator

Methods of data collection

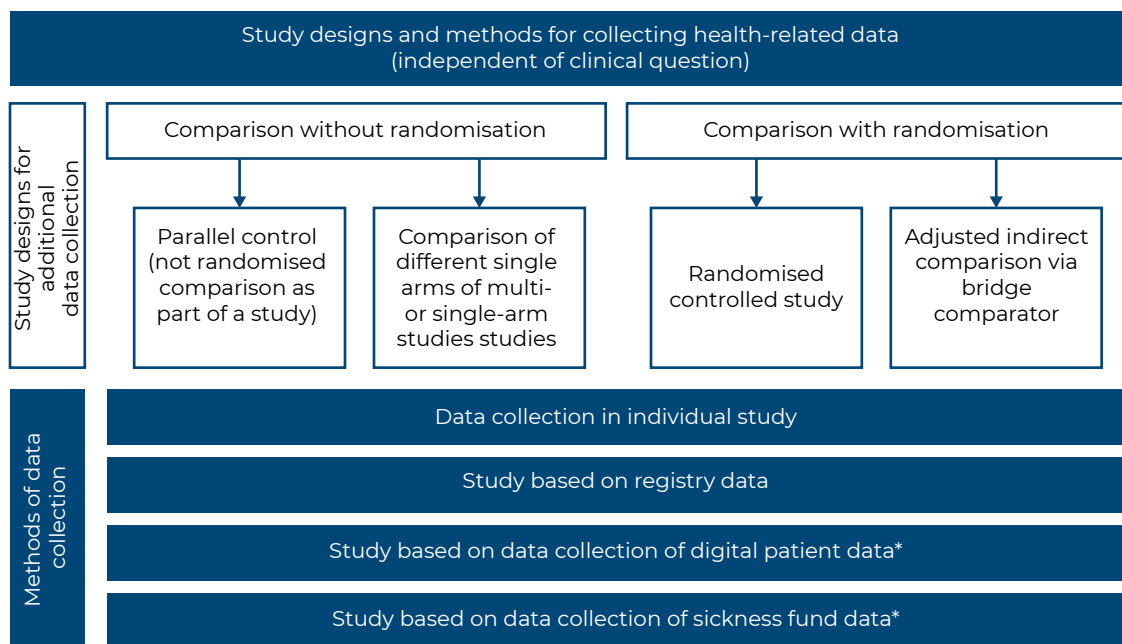| Data collection in individual study |
|---|
| Study based on registry data |
| Study based on data collection of digital patient data* |
| Study based on data collection of sickness fund data* |

Figure 2 Overview of possible study designs and data evaluation methods based on the IQWIG Rapid Report from 10.01.2020

(*not accepted by G-BA and IQWIG)

3.1 Study planning

As long as the evidence gap is not closed, G-BA cannot make a final decision on the extent of the patient-relevant additional benefit for the new product. In consequence, G-BA, IQWIG and supporting medical expert organisations are formulated to define a clinical study question for the extended application-accompanying data collection and the optimal study design.

It is recommended that pharmaceutical companies cooperate strongly with G-BA on the development of the study design for the extended application-accompanying data collection.

Overview study planning by G-BA:

From clinical study question to result:			
Formulation of the clinical study question	Formulation of the clinical study question based on the benefit assessment		
Decision for the optimal study design	Comparative study design without randomisation	Comparative study design with randomisation	Adjusted indirect comparison with common comparator
Study planning	Definition of the target study, study protocol, analysis plan	Study protocol, analysis plan	Study protocol, analysis plan for systematic reviews
Data collection	Retrospective/ prospective (outcomes and confounder)	Prospective (outcomes)	Retrospective
Analysis	Approaching structural equality through adjustment, group comparison	Structural equality through design, group comparison	Check: homogeneity, consistency, similarity
Interpretation	Interpretation of the results depending on the quality of the results achieved	Interpretation of the results depending on the quality of the results achieved	Interpretation of the results depending on the quality of the results achieved

Figure 3 Overview study planning (based on IQWIG Rapid Report from 10.01.2020)

3.1.2. The optimal study design:

Assuming that the registry fulfilled all criteria on data management and quality, IQWIG recommends two types of registry studies for the derivation of the extent of the patient-related benefit for the product.

We will summarise the most important key messages for both studies.

1. Routine-practice-related (versorgungsnahe) comparative studies without randomisation:
   — If comparative studies related to healthcare without randomisation are to be used for the benefit assessment, the study planning must ensure that the study conducted and the data collected are of the necessary quality to generate interpretable results.
   — The study protocol includes an analysis plan and emulation of a target study that defines the relevant overall clinical study question and ensures the collection of valid data for a confounder control.
   — The central aspect is the adjusting of confounders and the management of confounders.
   — In order to see outcome effects in studies without randomisation, it is important that data quality and the quality of the used analysis are high.
   — Even under high-quality requirements (for data, evaluation and reporting), it is generally no longer possible to derive results from comparative, care-related studies without randomisation as an indication of an effect.
   — Due to the inherent uncertainty of the results from comparative studies without randomisation, as a result of potentially unknown confounders, a statement on the benefit or harm of an intervention should only be derived from the effects observed in the study above a certain effect size; quantification of an additional benefit according to the legally prescribed extent categories requires corresponding effect sizes graded according to the size.
2. Routine-practice-related (versorgungsnahe) comparative studies with randomisation:
   — For comparative studies with randomisation, the optimal study design is a "pragmatic trial design".
   — The effort for a supply-related comparative study with randomisation will generally be lower than for a study without randomisation, given comparable data quality, since data collection and adjustment for the confounder control can be omitted.
   — Comparative studies with randomisation based on healthcare-related data are more powerful than those without randomisation; quantification of the additional benefit is likely to be more reliable.
   — Especially after approval, comparative studies with randomisation can be conducted with limited data collection ([large] simple trials) depending on the existing clinical question; an implementation in registries has additional potential to accelerate the studies and make them less complex (registry-based comparative studies with randomisation).

3.2. Data requirements:

In principle, the data to be collected must be suitable to close the evidence gap.
However, it must also be ensured that the closing of the evidence gap makes it
possible to derive the patient-relevant additional benefit for the product.

What data should be collected?

1. Data to measure efficiencies on the mortality level
2. Data to measure efficiencies on the morbidity level
3. Data to measure efficiencies on the quality of life level
4. Data to measure efficiencies on long-term safety
5. Other data that are suitable to close the evidence gap

The following are important terms related to data evaluation and analysis:

Term	Definition
Effect	An effect describes the difference measured in the context of comparative clinical studies for a target variable after the use of two (or more) interventions.
Data tool	The chosen instrument for data collection must be able to provide data in the necessary quality (e.g. validated HR-quality of life questionnaire).
Internal validity (high/low)	Internal validity is the extent to which a piece of evidence supports a claim about cause and effect within the context of a particular study.
External validity (high/low)	External validity is the validity of applying the conclusions of a scientific study outside the context of that study (transferability from a real-world context).
Structure equality	Harmonised patient groups, harmonised inclusion and exclusion criteria.
Effect size	Reliability of results is a characteristic of the result of a single study or a systematic overview/ meta-analysis. It denotes the confidence that a result found in the study(s) is close to the real result. The certainty of results from the assessment of the risk of bias of a study and the size of the statistical uncertainty.
Confounder	A confounder is a factor that is associated with an intervention (or exposure) as well as with the target criterion of a study. The English term is also often used in German. If, for example, the people in a group in which therapy A is used are younger than those in the group in which therapy B is used, it is difficult to decide to what extent less frequent heart attacks in group A are due to the therapy or the group's younger age. Age is a confounder. Countermeasure: Randomisation minimises such inequalities; known confounders and those found in the study can be taken into account by using suitable statistical methods (adjustment).
Endpoint rating	To define the extent of the overall additional benefit as the final AMNOG result, IQWIG is rating every single endpoint based on its statistical importance (p-value; Hedges' g, confidence interval, statistical methodologies). Endpoint rating: a) Evidence (Beleg) of the endpoint: strong rating b) Hint (Hinweis) of the endpoint: medium rating c) Indication (Anhaltspunkt): weak rating
Dramatic effect	If the course of a disease is certainly or almost certainly predictable, and no treatment options are available to influence this course, then proof of a benefit of a medical intervention can also be provided by the observation of a reversal of the (more or less) deterministic course of the disease in well-documented case series of patients. If, for example, it is known that it is highly probable that a disease leads to death within a short time after diagnosis, and it is described in a case series that, after application of a specific intervention, most of those affected survive for a longer period of time, then this "dramatic effect" may be sufficient to provide proof of a benefit (relative risk [RR] threshold = 5–10).

3.3. Registry requirements:

The quality of the data correlates significantly with the quality of the registry. Based on the Rapid Report from IQWIG, registries for the extended application-accompanying data collection must be indication-specific. If registries exist, the pharmaceutical company can use these registries and must not create a new one.

Selected registry quality overview: (Please be aware that in this checklist, we present selected overall criteria. Special criteria based on the individual indication must be additionally considered.)

1. Detailed register description (protocol) standardisation
2. Exact definition/operationalisation of exposures, clinical events, endpoints and confounders
3. Current data plan/coding manual
4. Use of standard classifications (e.g. ICD-10) and terminology (e.g. MedDRA)
5. Use of validated standard survey instruments (questionnaires, scales, tests)
6. Training on data collection
7. Implementation of an agreed disease-specific core data set ("core data set")
8. Use of exact dates for the patient (e.g. birth, death, pregnancy)
9. Use of exact dates for the disease (e.g. definitive diagnosis, clinically relevant events)
10. Use of exact dates for important examinations
11. Use of exact dates for treatments/interventions (e.g. for drugs, start/stop date, dose, dose changes)
12. Achievement of the recruitment target/sampling
13. Clearly defined inclusion and exclusion criteria for registry patients
14. Completeness of registry patients (full survey or representative sample)
15. Strategies to avoid unwanted selections in patient inclusion to achieve representativeness and validity of the data collection
16. Completeness of the data at each time of the survey (loss-to-follow-up, drop-outs)
17. Completeness of the survey times
18. Accuracy of the data
19. Data consistency over time
20. Source data verification (e.g. for 10% of randomly selected patients per survey centre)
21. Registry monitoring through internal and external audits
22. QM system (if necessary, with regular collection of quality indicators)
23. Standard Operating Procedures (SOPs) for data collection
24. Transparency of a registry (including financing, decision-making channels, conflicts of interest)
25. Scientific independence

4.0 Consideration of the extended application-accompanying data collection in terms of strategic AMNOG planning

The extended application-accompanying data collection as a new tool has a big impact on the results for the AMNOG process for new pharmaceutical products. It is important that pharmaceutical companies include this tool in their market access plans.

Extended application-accompanying data collection; the most important implications for companies:

— Market entry time of the new product
— Prescription behaviour of physicians
— Using of pre-AMNOG tools (e.g. selective contracting)
— Reimbursement price negotiation and reimbursement price expectations
— Financial and personal resources
— Expected uptake of the product
— Cost-saving/depression activities by regional sickness funds
— Longer overall AMNOG assessment time

As per law, the G-BA can decide to start with the extended application-accompanying data collection:

a) From the first day the product is available on the German market (market authorisation)

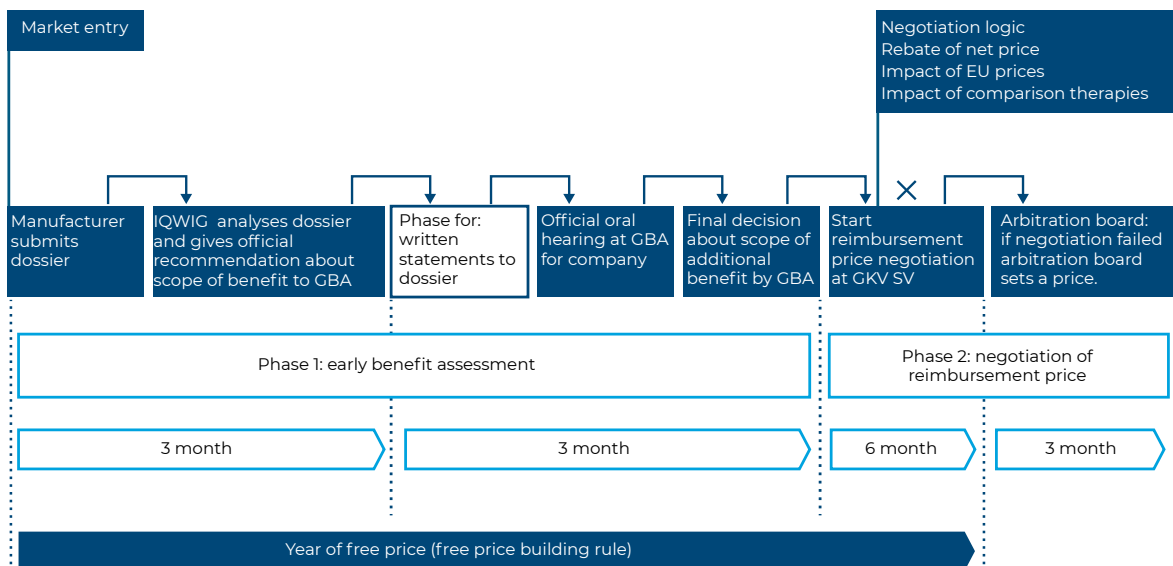b) After the "oral hearing" as part of the final benefit assessment decision

Figure 4 Overview of the normal AMNOG process without the extended application-accompanying data collection

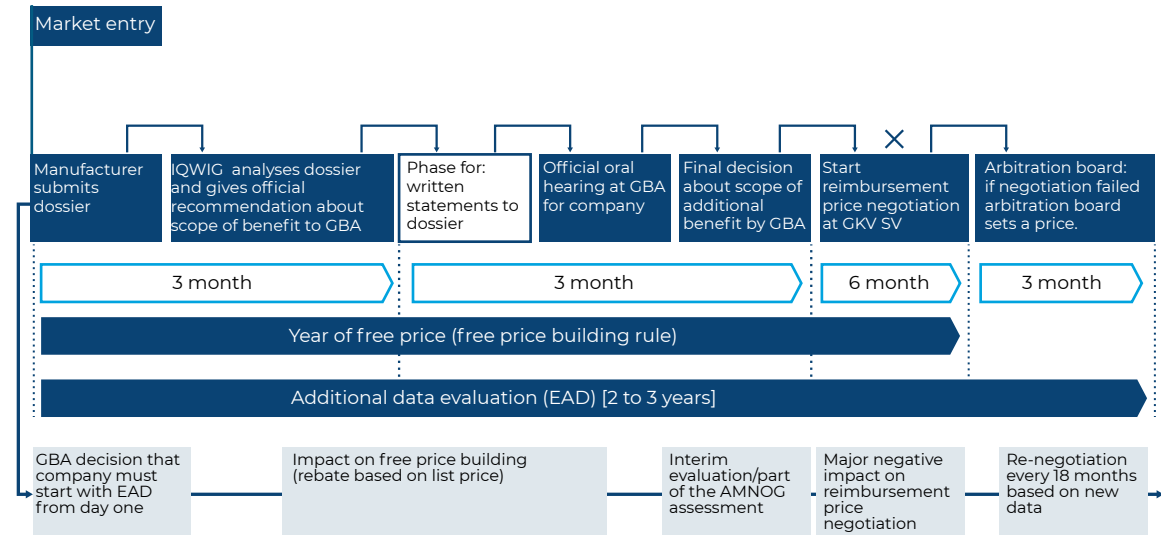## 4.1. Case study 1 (EAD requirement from day 1: Market authorisation)

Figure 5 The AMNOG process with the extended application-accompanying data collection from day 1 (marketing authorisation)

In this scenario, the pharmaceutical company has received the request to start with the extended application-accompanying data collection from day 1 (market authorisation). This has several market-access-related implications for the company.

Risk	Market access consequence	Tactics
Free price building in year 1	Price cut of list price at an early point in time	Definition of a value-based access price Definition in alignment with the payer
Dossier	Uncertainties for dossier writing	Strengthening of available evidence through additional analysis (statistical, patient conjoint)
Pre-AMNOG contracts	Difficult to negotiate pre-AMNOG contracts to secure uptake and prescriptions	Start with contract negotiation before day 1.
Overall AMNOG rating	More than a "non-quantifiable additional benefit" is not possible.	Active communication of the G-BA resolution to stakeholder. "Non-quantifiable" is, in general, not negative and not positive. It is a neutral decision and says nothing about the value of the product.
Reimbursement price negotiation	Reimbursement price negotiation with GKV SV will be difficult. Premium price not possible. Limited mix price in the worst case.	Innovative negotiation strategy: — Volume agreements — No VA strategy — § 130 c SGB V strategy
AMNOG strategy	Overall AMNOG process strategy will be difficult, especially the derivation of value argumentation, unmet and medical need.	The company should start with AMNOG process strategy development a minimum of 12 months before day 1.

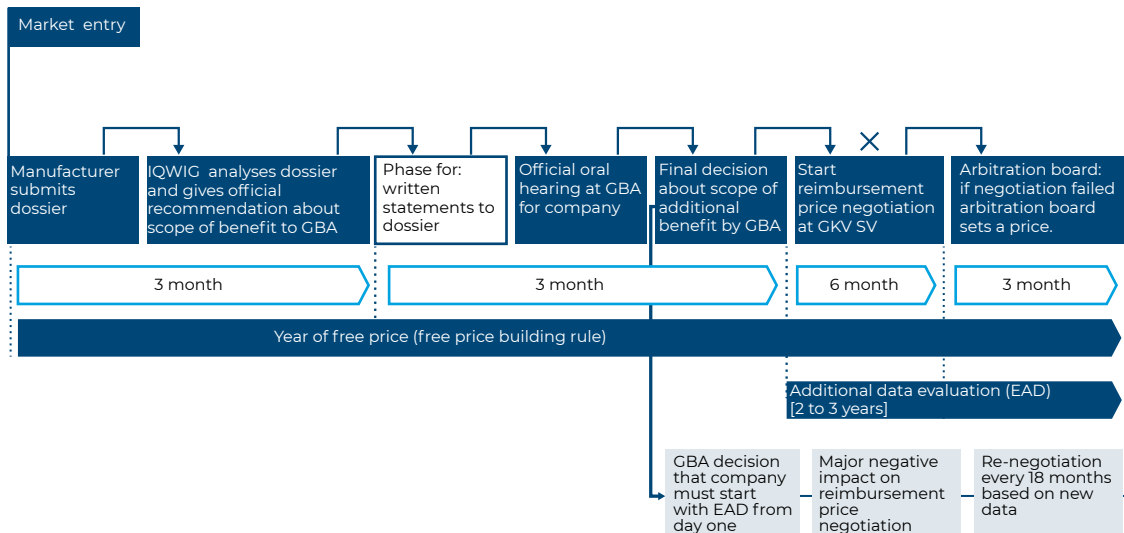## 4.2. Case study 2 (EAD requirement from month 6 after oral hearing)

Figure 6 The AMNOG process with the extended application-accompanying data collection from month 6

In this scenario, following the oral hearing, the G-BA has decided that by month 6, the company has to enter the extended application-accompanying data collection. The advantage of this scenario is that the company can participate in the full 12 months of the free pricing rule.

Risk	Market access consequence	Tactics
Free price building in year 1	No risk.	
Dossier	Opportunity to close the evidence gap.	Strengthening of available evidence through additional analysis (statistical, patient conjoint).
Pre-AMNOG contracts	Negotiation possible.	Especially high-cost drugs should use this opportunity. Contract duration no longer as at the first GKV SV negotiation meeting.
Overall AMNOG rating	More than a "non-quantifiable additional benefit" is not possible.	Active communication of the G-BA resolution to stakeholder. "Non-quantifiable" is, in general, not negative and not positive. It is a neutral decision and says nothing about the value of the product.
Reimbursement price negotiation	Reimbursement price negotiation with GKV SV will be difficult. Premium price not possible. Limited mixprice in the worst case.	Innovative negotiation strategy: — Volume agreements — No VA strategy — § 130 c SGB V strategy
AMNOG strategy	The derivation of value argumentation, unmet and medical need will be complex. Management of the evidence gap is necessary.	The company should start with AMNOG process strategy development a minimum of 12 months before day 1.

Usually, companies know their clinical data at a very early stage. If an evidence gap is detected, the creation of a registry/or the entry into a suitable existing registry should start early, before the AMNOG process. This can significantly minimise the risk of a low reimbursement price. Furthermore, the G-BA can consider first results in its final decision on the benefit assessment.

5.0 Chances and risks of the extended application-accompanying data collection

In this chapter, we will analyse the potential chances and risks of the extended application-accompanying data collection for a pharmaceutical company.
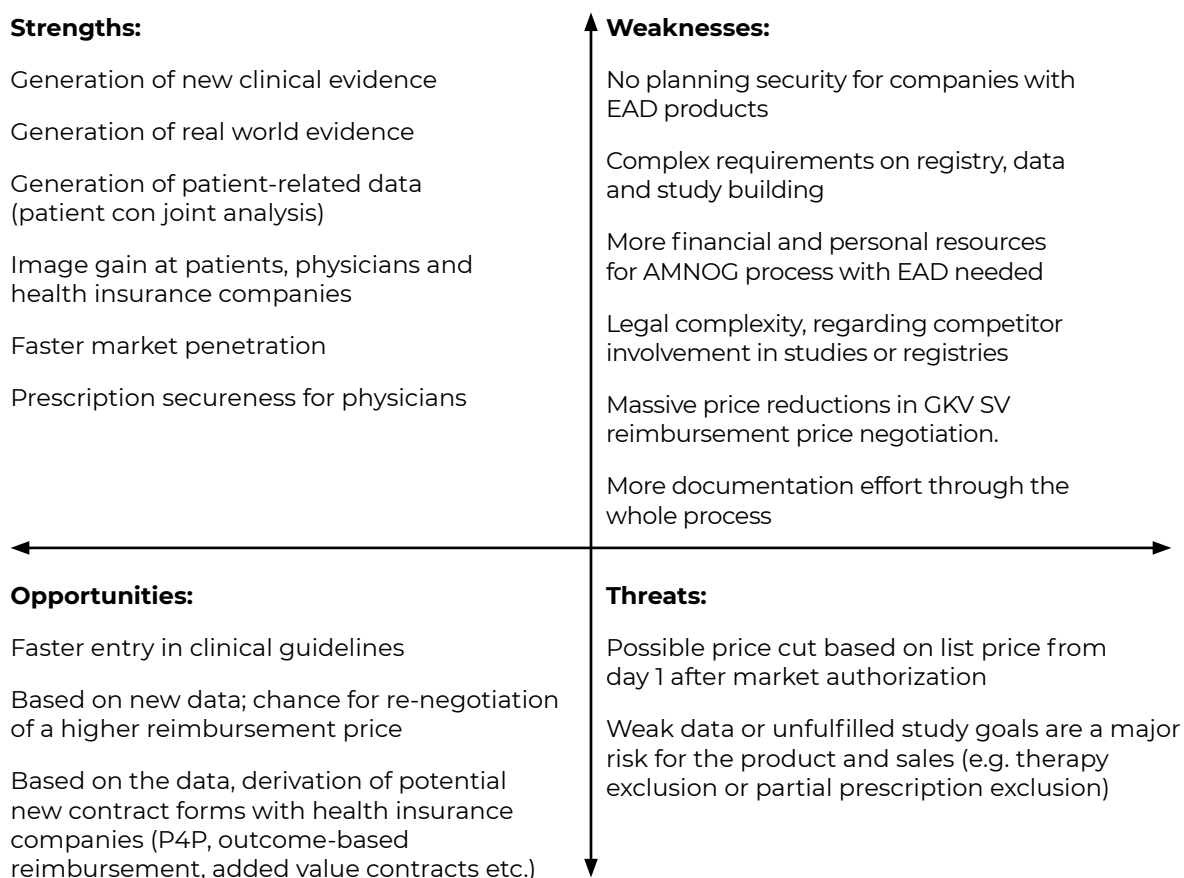
Strengths:

Generation of new clinical evidence

Generation of real world evidence

Generation of patient-related data (patient con joint analysis)

Image gain at patients, physicians and health insurance companies

Faster market penetration

Prescription secureness for physicians

Weaknesses:

No planning security for companies with EAD products

Complex requirements on registry, data and study building

More financial and personal resources for AMNOG process with EAD needed

Legal complexity, regarding competitor involvement in studies or registries

Massive price reductions in GKV SV reimbursement price negotiation.

More documentation effort through the whole process

Opportunities:

Faster entry in clinical guidelines

Based on new data; chance for re-negotiation of a higher reimbursement price

Based on the data, derivation of potential new contract forms with health insurance companies (P4P, outcome-based reimbursement, added value contracts etc.)

Threats:

Possible price cut based on list price from day 1 after market authorization

Weak data or unfulfilled study goals are a major risk for the product and sales (e.g. therapy exclusion or partial prescription exclusion)

Figure 7 SWOT analysis for the AMNOG process with the extended application-accompanying data collection (EAD)

What helps to manage the risks and chances of the AMNOG process with a potential EAD?

— A clear business case, with different pricing assumptions
— A deep data analysis about the potential risk of an evidence gap
— A value analysis based on patient, physician, payer and authority perspectives for the product, including the value innovation surcharge algorithm
— A value-based pricing concept
— Strategic scenarios (e.g. change of launch frequency)
— Use of possible alternative temporary market entry models
— A very experienced team (AMNOG experience, value management experience, registry experience, pricing experience, deep understanding of the German health system to manage post-AMNOG: possible regional prescription barriers)

If a company does not meet the EAD requirements, there is a risk of exclusion from the supply. That means the drug is no longer reimbursed and may no longer be prescribed.

6.0 Chances and risks of the EAD for reimbursement price negotiations

Besides the major impact of the EAD on the AMNOG benefit assessment, the second major impact of the EAD is on the reimbursement price. The overall political intention of the extended application-accompanying data collection (EAD) tool was to reduce the medication prices, especially those of high-cost drugs (e.g. orphan drugs and ATMP).

Currently, the development of a reimbursement price is mainly based on the following three pillars:

1. The extent of the additional benefit defined by the G-BA (minor, major, none, non-quantifiable, etc.)
2. European reference prices
3. Prices of comparative therapy (not in the case of orphan drugs)

For EAD products, new reimbursement price concepts are currently under discussion.

6.1. Annuity reimbursement model ("Annuitätenmodell")
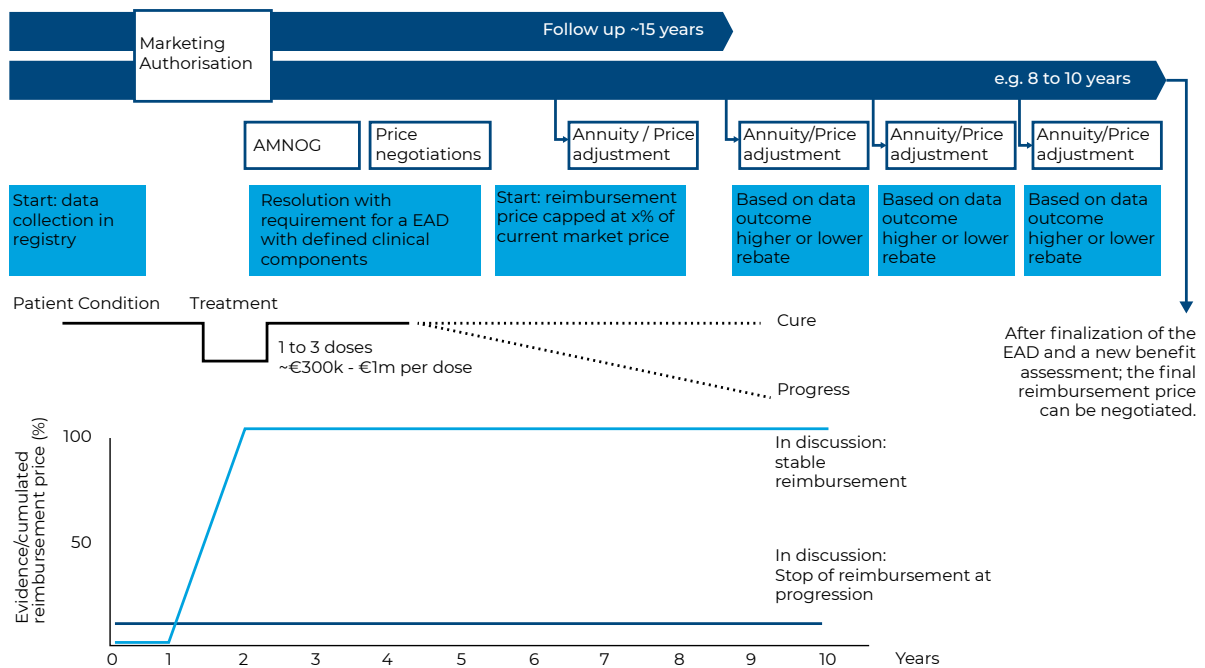

Figure 8 Annuity reimbursement model (source I.f.G.V.)

The annuity reimbursement model is currently under discussion as a new reimbursement (outcome-based) model for high-cost treatments, especially ATMPs and orphan drugs with EAD resolution through the G-BA. After EAD resolution, the company has 18 months to initiate a registry, and the G-BA must be notified about the successful initiation. Based on a clinical publication plan, the company must submit clinical interim analyses every 18/x months. Based on the outcome, the reimbursement price will be adjusted.

6.2. Dynamic evidence price model:

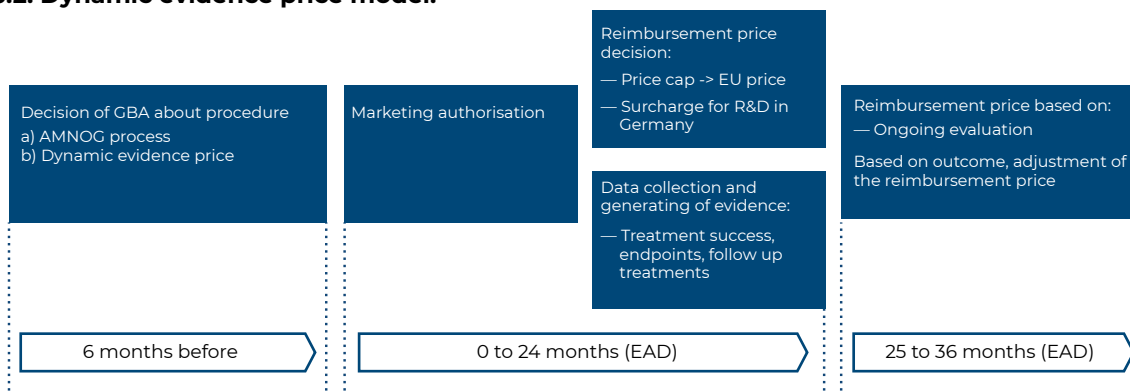| Decision of GBA about procedure a) AMNOG process b) Dynamic evidence price	Marketing authorisation	Reimbursement price decision: — Price cap -> EU price — Surcharge for R&D in Germany	Reimbursement price based on: — Ongoing evaluation Based on outcome, adjustment of the reimbursement price
		Data collection and generating of evidence: — Treatment success, endpoints, follow up treatments	
6 months before	0 to 24 months (EAD)		25 to 36 months (EAD)

Figure 9 Dynamic evidence price model (Source I.f.G.V.)

The dynamic evidence price model is a proposal from some health insurance companies in Germany. It is currently under discussion but has not been officially implemented. In this model, the outcome-based rebate component is much stronger than in the annuity model (see 6.1.). The price cap, based on the EU price, was especially a major disadvantage for many companies.

The legal background for development of the reimbursement price and a reimbursement price negotiation is very strong. Massive changes in the GKV SV reimbursement negotiation logic cannot be implemented easily and quickly by law.

Currently in force:

— The standard procedures for reimbursement price development are active
— Mixed pricing logic is most commonly used
— Use of innovative pricing design (e.g. no — VAM strategy; volume agreements, etc.)

7.0 Post-AMNOG: market penetration with EAD — barrier or chance?

It is risky to think that, after the AMNOG process and GKV SV reimbursement negotiation, the job is done and the product can be safely prescribed and reimbursed. Germany has 105 sickness funds and is segmented in 17 KV (physician associations).
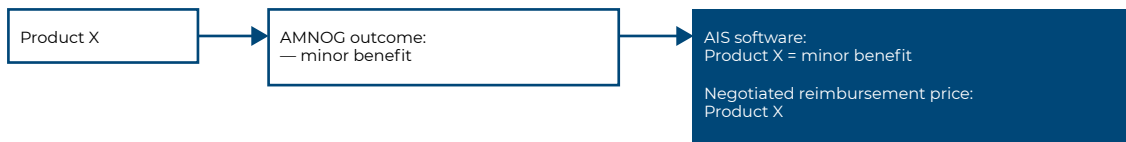
Problem 1:

Regardless of the AMNOG process and reimbursement price negotiation, each health insurance company has its own strategies and tools. They can recommend the prescriptions or use various tools to put the doctors under pressure so that AMNOG products may only be prescribed to a limited extent or only under specific conditions. If physicians do not follow these requirements and restrictions, health insurance companies threaten with regression.

Problem 2:

Since March 2020, a new information tool has been implemented by the G-BA: the "medication information system" (Arzneimittelinformationsystem [AIS]). The aim of this tool is to inform physicians on the outcome of the benefit assessment. The information will be transferred directly into the physicians' prescription software.

Health insurance companies, especially, can use this tool to guide physicians in their prescription behaviour. For pharmaceutical companies, it is a major risk that negotiated prices are available for physicians (in the worst case for each sub-population).

Example 1:

Product X	→	AMNOG outcome: — minor benefit	→	AIS software: Product X = minor benefit Negotiated reimbursement price: Product X

Example 2:

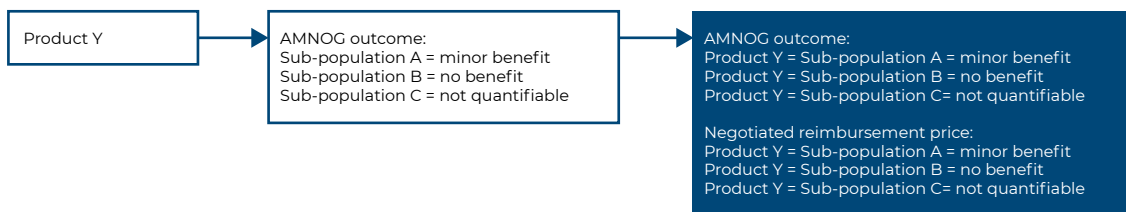| Product Y	→	AMNOG outcome: Sub-population A = minor benefit Sub-population B = no benefit Sub-population C = not quantifiable	→	AMNOG outcome: Product Y = Sub-population A = minor benefit Product Y = Sub-population B = no benefit Product Y = Sub-population C = not quantifiable Negotiated reimbursement price: Product Y = Sub-population A = minor benefit Product Y = Sub-population B = no benefit Product Y = Sub-population C = not quantifiable

Figure 10 Transfer from G-BA AMNOG assessment results into prescription software

Problem 3:

In addition to problems 1 and 2, the EAD is now added. It is to be expected that regional health insurance companies and KVs (regional head physician association) influence physicians to stop or reduce prescription of EAD products. The argument could be that the product has first passed the EAD to prove its efficiency versus a comparative therapy. On a legal basis, health insurance companies could argue that until the end of the EAD and the final decision through G-BA, the product is not economic based on § 12 SGB V(Wirtschaftlichkeitsgebot).

The first tools to guide prescription behaviour are in discussion:

— "Single cost agreement" (Einzelfallkostenübernahme Antrag) via health insurance companies
— "Second opinion procedure" (Zweitmeinungsverfahren)
— Strong quality criteria as directive (Qualitätssicherung–Richtlinie)

In summary, we can see that the EAD is an additional barrier to the prescription of the product in daily practice, especially if it is a high-cost product.

8.0 The right team, the right strategy

The AMNOG process in Germany is one of the most complex benefit assessment procedures in Europe.

In the AMNOG process, complex legal, medical and health economics requirements must be taken into account. The process is strictly formalistic. The few interaction options with the G-BA are extremely demanding and have to be prepared extremely well. In addition, the GKV reimbursement price negotiation comes from a team which requires a high level of medical, legal and negotiation skills.

A successful AMNOG outcome and a successful reimbursement price negotiation are critical for the business of most companies:

1. Germany has the biggest market in Europe.
2. Germany is the No. 1 launch market in most cases.
3. Seventeen countries directly reference the German reimbursement price (EU price impact).

Furthermore, we now have an additional highly complex tool to manage – the EAD.

This new process can therefore only be managed by a team of very experienced experts and by consultants for registries as important members of the project team for the extended application-accompanying data collection.

Market Access Manager with AMNOG and GKV negotiation experience	Lead for the AMNOG project; value story, AMNOG strategy, dossier strategy, pricing and negotiation strategy
In case of EAD, special consultants with deep experience for registries	Must build the registry, develop the EAD strategy, develop the registry study, handle recruitment, etc.
Medical expert	Offers support for all medical questions and study questions
Internal/external biostatistician (ideally with AMNOG experience)	He/she must defend the dossier and clinical statistic questions in the "oral hearing"
Dossier writer	Writes the dossier
External consultant for pricing	Develops the negotiation strategy with the market access manager
External lawyer with GKV SV experience	Part of the negation team at GKV SV

The right AMNOG strategy:

It is recommended to structure the AMNOG process in different parts. In principle, it is also strongly recommended to start preparing the AMNOG strategy at least 12 months before marketing authorisation.
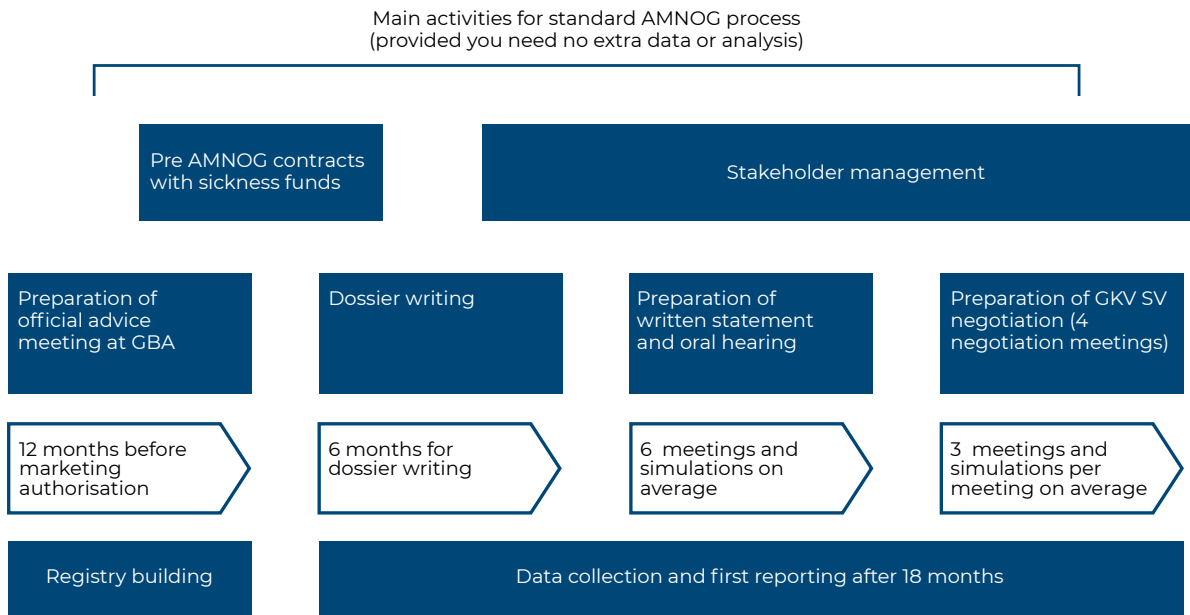
Strategy building for an AMNOG process:

Main activities for standard AMNOG process
(provided you need no extra data or analysis)

Pre AMNOG contracts with sickness funds	Stakeholder management		
Preparation of official advice meeting at GBA	Dossier writing	Preparation of written statement and oral hearing	Preparation of GKV SV negotiation (4 negotiation meetings)
12 months before marketing authorisation	6 months for dossier writing	6 meetings and simulations on average	3 meetings and simulations per meeting on average
Registry building	Data collection and first reporting after 18 months		

Figure 11 The most important work packages for an AMNOG

Clinical data — Evidence GAP

Pricing expectations — EAD risk

AMNOG strategy

Dossier story — Health care unmet need

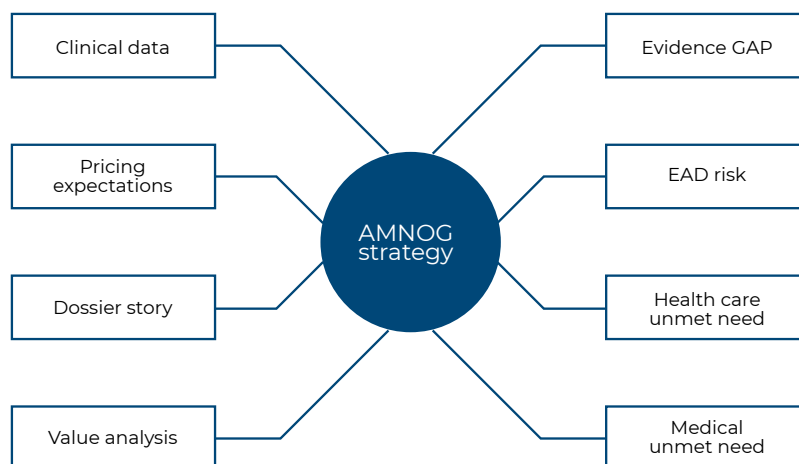Value analysis — Medical unmet need

Figure 12 The most important impact factors for building a successful AMNOG strategy

9.0 Partner of choice: Why working with Cerner Enviza^{SM}/ZEG-Berlin is the key to success

It is recommended to contact the G-BA early enough so that a first counselling interview can be conducted. This means that even in a very early phase, these discussions with the G-BA can already be crucial for a successful submission. At this early stage, it is therefore highly recommended to involve an expert for registry studies to be prepared for the upcoming discussions. It is critical not to miss relevant topics for the following discussions with the G-BA. Moreover, key points should be discussed very soon, such as the following:

— Is a comparative treatment available?
— Do you have enough information about the natural history of the disease? If you do not expect to have enough patients to include, please think about collecting data before the launch so that historical comparison data will be available. The additional benefit has to be quantifiable, and it is the responsibility of the product owner to find a way to do this.
— Is a registry already established? Please also keep in mind that registries do not usually include the additional information that the G-BA wants to see for the submission, e.g. quality of life/PROs, morbidity or adverse events. Furthermore, it is not sufficient to focus only on the assessment of safety either.
— Do you plan to create a product-related registry? If so, then please note that the required evidence cannot be provided with this kind of registry, as comparative data are needed.
— When you start to build or use an existing registry, please validate the quality, as high quality is needed. In addition, it is important to explain why and how you have built the registry and how you can best meet your objectives by using the chosen registry.

This shows that there are a lot of things to consider, and therefore a gap analysis carried out together with Cerner Enviza's and ZEG-Berlin's registry experts is recommended to further define the strategy. Working together with our experienced registry experts can be the key for successful submissions. For that purpose, Cerner Enviza offers a full package of services along the complete pathway of the AMNOG process:

— Planning of studies (before the discussions with the G-BA start): design of approval studies, keeping relevant endpoints for the EAD in mind
— Conducting counselling interviews together with Cerner Enviza experts: strategic implications/identifying data gaps and conducting a risk analysis
— Evaluation of the recommended study design
— Execution of the EAD and consultancy
— Support in creating required documents
— Advanced data analyses and assessment of the value (medical and HEOR need) for the discussions with the GKV Spitzenverband (The National Association of Statutory Health Insurance Funds)
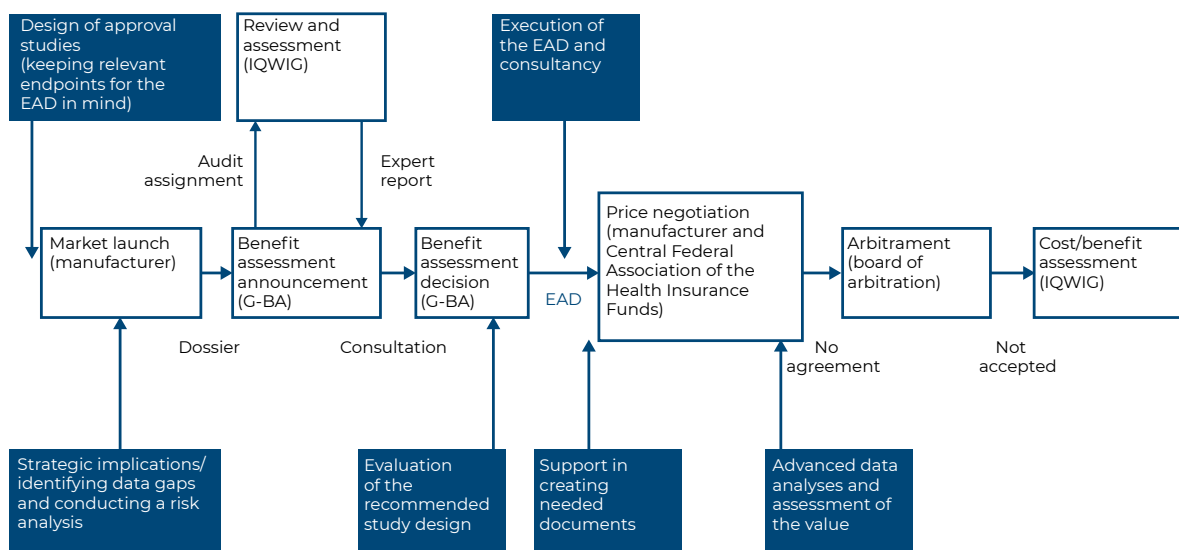

Figure 13 Illustration based on source https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Broschueren/Broschuere_Die_Spreu_vom_Weizen_trennen_-_Das_Arzneimittelmarktneuordnungsgesetz.pdf

The basis for these listed services is Cerner Enviza's strong expertise in developing and maintaining registries as well as in conducting registry studies. Cerner Enviza/ZEG-Berlin has a proven track record, and – maybe even more importantly – clients trust Cerner Enviza/ZEG-Berlin. Two examples can be found below:

Study	First-line low- to intermediate-risk Acute Promyelocytic Leukemia (APL) study using existing disease registries	Long-term safety of different treatment options in patients with moderate to severe psoriasis
Objectives	PRAC requested PASS Treatment regimens in newly diagnosed low- to intermediate-risk APL patients in real world clinical settings Evaluation of effectiveness and safety of different chemotherapy-free treatment dosing regimens in newly diagnosed low- to intermediate-risk APL patients	PRAC requested PASS Assessment of risks and comparison between different treatment options for psoriasis patients starting new treatment Evaluation of psoriasis patients' characteristics receiving different treatment Evaluation of all adverse events and information obtained regarding pregnant and lactating women
Countries	Six EU countries: France, Germany, Italy, Poland, Spain, Portugal	Three EU countries: Germany, Spain, United Kingdom/Ireland
Number of Registries	Up to eight EU leukemia registries	Three EU psoriasis registries
Tasks	Data transfer specifications and data mapping for all participating registries Setup and maintenance of pooled study database Quality review of the received data and summary reports to the sponsor after each data transfer Yearly interim results	Development of the study protocol Preparation of annual progress report based on yearly/bi-yearly registry reports Quality review of the received data and summary reports to the sponsor Data transfer specifications and data mapping for all participating registries Pooled analysis of the registry data
Duration	Yearly data transfers and analysis from the seven registries over five years	Eight years of study duration with annual progress reports and final data analysis

10.0 Three key takeaways

The key takeaways in terms of the extended application-accompanying data collection are:

1. **You should contact an expert for registries and registry studies early enough to create a successful strategy for your HTA submission.**
2. **A comparison is mandatory.**
3. **High-quality registries and expertise in conducting registry studies are needed.**

For more information, please contact your registry experts:

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About Cerner Enviza

Cerner Enviza aims to accelerate the discovery, development and delivery of extraordinary insights and therapies to improve everyday health for all people globally. By combining decades of innovation, life sciences knowledge and collaborative research, Cerner Enviza provides data-driven solutions and expertise that helps bring remarkable clarity to healthcare's most important decisions. For more information on Cerner Enviza, visit **www.cernerenviza.com**.

For more information, please contact **info@cernerenviza.com.**