2025

German Benefit Assessment - White Paper

LATEST METHODOLOGICAL REQUIREMENTS IN THE GERMAN BENEFIT ASSESSMENT

CROSS-COMPANY COLLABORATION

Contents

Preface – Content and Acknowledge

With the introduction of the German Act on the Restructuring of the Pharmaceutical Market (AMNOG) in 2011, new drugs in Germany are subject to a comprehensive Health Technology Assessment (HTA) and subsequent reimbursement agreements as soon as they are launched and whenever their indications are expanded. The aim is to determine the added benefit of the new drug compared to the current standard of care.

The assessment is based on Section 35a of the German Social Code Book V (SGB V), the rules of procedure of the Joint Federal Committee (G-BA), the highest decision-making body in the German health care system, and the methodology developed by the independent Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefits and harms of medical interventions for patients.

Since its introduction, more than 429 new medicines have been subjected to the German benefit assessment. In total, more than 1,050 procedures have been carried out. The AMNOG is designed to ensure a comprehensive assessment. To achieve this, the advantages and disadvantages of new medicinal products and medical procedures are assessed, for example by comparing the new medicinal product with the standard of care in Germany, regardless of whether it is a drug or another intervention, such as surgery, different drugs or surgical procedures. Trials are selected and assessed using evidence-based methods. This international standard method is used to assess the reliability of available knowledge.

It is important to note that the methods and decision-making standards are also being developed and updated to facilitate evidence-based decision-making on investigations and treatments. This White Paper outlines relevant specifics and selected innovations that have already occurred or may occur in the future in connection with the implementation of EU-HTA and the expected maintenance or adaptation of IQWiG's methodology. An overview of the content of the individual chapters is provided below. For more detailed information, please refer directly to the relevant chapter.

1. Overview and challenges of EU-HTA with a focus on German benefit assessment

This section outlines the introduction and impact of the European Joint Clinical Assessment (JCA) under Regulation (EU) 2021/2282, which aims to enhance patient access to innovative health technologies and reduce duplication of efforts in HTA across the EU. Starting in 2025, new medicines, including oncology and Advanced Therapy Medicinal Products (ATMPs), will undergo clinical assessments at the European level, with orphan drugs assessed by 2028 and all other medicines by 2030. Despite this harmonization, national HTA authorities may still perform complementary evaluations. For Germany, the JCA report, though crucial, may not be available by the time the national dossier is submitted. Therefore, and due to potential additional evidence requests the creation of a "delta dossier" to address any missing information might be neccessary. The timelines for JCA are aligned with the EMA process, and the German benefit assessment will incorporate both the national and JCA dossiers. The section discusses the current developments and uncertainties in the system as it adapts to the new EU regulations, recommending close collaboration between the health technology developer (HTD) and national AMNOG teams to ensure alignment with German PICO requirements. As the system evolves, ongoing monitoring and adaptation are essential to address emerging challenges.

2. Appropriate comparator therapy

This section discusses the process of determining the Appropriate Comparator Therapy (ACT) within the German healthcare system, as outlined by the G-BA. The ACT is used as the standard comparator for evaluating new treatments and is essential for the benefit assessment process. Key criteria for determining the ACT include marketing authorization for the relevant indication, reimbursement by Statutory Health Insurance (SHI), previous G-BA resolutions, and alignment with the current medical standard. The ACT may change throughout the benefit assessment process, such as after early consultations, during ongoing studies, or after the submission of the benefit dossier. Various factors, including new scientific evidence and regulatory changes, can trigger modifications to the ACT, impacting all treatments within a specific substance class. This section emphasizes the importance of staying informed and prepared for potential ACT changes to mitigate risks, offering strategies for pharmaceutical companies, including proactive monitoring of evidence, early engagement for study design, and ongoing adjustments to strategies. Additionally, the evolving landscape of the EU Health Technology Assessment (EU-HTA) is discussed, highlighting the complexity of defining comparators across different member states.

3. Pre-specified HTA analyses plan

This section focuses on the importance of pre-specification in benefit assessments under the AMNOG process, emphasizing the distinction between pre-specified analyses and post-hoc analyses in clinical trials. Pre-specification, outlined in the study protocol or Statistical Analysis Plan (SAP), is crucial for maintaining transparency and integrity in clinical data analysis. Key components of the German HTA include the study population, subgroup analysis, endpoints, safety analysis, and statistical methodologies. The G-BA's requirements guide the structure of analyses, such as focusing on patient-relevant outcomes and using relative risk (RR) or hazard ratios (HR) for effect size estimation. The section also discusses the implications of the evolving EU-HTA framework, which may lead to adjustments in analysis methods, particularly with indirect comparisons and single-arm trials. Recommendations are provided for optimizing pre-specification and aligning with G-BA requirements, emphasizing early planning, adherence to pre-specified analyses, and proactive G-BA engagement to ensure a successful benefit assessment process.

4. Actuality of data cuts in German HTA

This section discusses the role and requirements of data cuts in the German benefit assessment process under AMNOG. A data cut refers to a point in time when clinical trial data is considered sufficient for analysis to answer the study objectives. The section distinguishes data cuts from other types of analyses, such as blinded or interim analyses. It emphasizes the need for a benefit assessment dossier to describe all planned data cuts, including those requested by regulatory authorities, and to provide clear justifications for any excluded or non-relevant data cuts. The focus of the G-BA is on the most mature data cut, with incomplete or outdated data cuts potentially affecting the perceived completeness of the submission. The submission of data cuts up to three months prior to dossier submission is mandatory, and later submissions may be possible as part of a written statement. The section also highlights the importance of aligning regulatory and HTA data to minimize inconsistencies and ensure comprehensive, reliable data. It provides recommendations for

managing and presenting data cuts to optimize the benefit assessment process, ensuring a high-quality dossier that supports better decision-making.

5. Patient-reported outcomes

This chapter addresses the requirements for patient-reported outcomes (PRO) in the German HTA process. PROs that reflect symptoms and health-related quality of life (HRQoL) are crucial for benefit assessment and can provide significant value, provided that the instruments used meet the same methodological standards for study design, data analysis, and evaluation as other patient-relevant outcomes. This includes the use of psychometrically validated instruments, response rates above 70%, and a universal clinical relevance threshold of ≥ 15% of the scale range for all PRO responder analyses. Alternatively, continuous data analyses may be employed. In that case, the relevance of PROs should be assessed using a standardized mean difference (SMD), specifically Hedges' g, with an irrelevance threshold of 0.2.

6. Meta-analysis in German HTA

This section discusses the use of meta-analysis in the German benefit assessment process for evaluating the added benefit of new medical treatments. Meta-analysis, which synthesizes results from multiple studies, is crucial for drawing robust conclusions about the effectiveness of interventions. The process includes key methodological considerations such as defining the population, intervention, and relevant endpoints, and ensuring the quality of included studies. Meta-analyses must follow IQWiG's guidelines, utilizing random effects models and appropriate statistical methods like the Knapp-Hartung and Paule-Mandel approaches. The results are presented in a comprehensive manner, including forest plots and assessments of heterogeneity. The section highlights the importance of high-quality studies and addresses challenges in small study numbers, where Bayesian approaches may be employed starting in 2024. The use of meta-analysis provides statistical power, enhances precision, and facilitates the demonstration of added benefits in benefit assessments. Recommendations emphasize the need to adhere to IQWiG’s methods, consider studies beyond regulatory approval, and prepare for the adoption of Bayesian meta-analysis in future assessments.

7. Quantification of an added benefit without Head-to-Head Data – Historical comparisions

This section discusses the use of historical comparisons in the German benefit assessment process when only single-arm trials are available for a new drug. Historical comparisons are essential for meeting the G-BA’s requirements when randomized controlled trials (RCTs) are not possible. Key acceptance criteria include study similarity, confounder adjustment, larger sample sizes, dramatic effect sizes, and the use of serious endpoints. The most suitable use cases for historical comparisons are diseases with severe outcomes, where substantial differences in treatment effects can be observed. The section highlights the specific role of historical comparisons in orphan drug status cases, where even without clear evidence, a non-quantifiable added benefit is regularly granted. Despite the challenges and strict evaluation by IQWiG and the G-BA, historical comparisons can still provide valuable evidence in the absence of RCTs, particularly for rare diseases and innovative therapies, potentially enhancing the treatment's value proposition. Recommendations emphasize that while proving an added benefit may be difficult, historical comparisons remain a crucial tool for benefit assessments.

8. Definition and validation of Surrogate Endpoints

This chapter discusses the validation of surrogate endpoints within the benefit assessment process in Germany. It provides an overview of accepted surrogate endpoints and highlights the challenges in fulfilling the requirements for the formal validation of additional surrogate endpoints. Methodological and practical considerations for surrogate endpoint validation are provided, including examples from previous benefit assessments. An outlook to EU-HTA is provided as well as recommendations and conclusions. Importantly, it is recommended to consider the acceptance of endpoints for German HTA already at study planning stage (e.g., by taking advantage of early consultations including G-BA advice). Due to the strict requirements for surrogate endpoint validation, it is advisable to rely on accepted endpoints whenever possible.

9. Routine Practice Data Collection for the use of new pharmaceuticals

Some medicinal products, including those with conditional marketing authorizations, those authorized under exceptional circumstances, and orphan drugs, receive limited clinical trial data upon marketing authorization but still obtain approval from the CHMP and the European Commission (EC). Despite insufficient data for benefit assessment in Germany, these products undergo a benefit assessment by the G-BA. In such cases, the G-BA may require the collection of real-world data to compare the product with its defined treatment comparators. This data helps enhance the evidence for benefit assessment, including its performance in daily practice.

Routine Practice Data Collection (AbD), initiated in 2020, involves gathering data through disease registries or newly established data collection methods. The information collected is crucial for assessing the benefits and potential risks of products, which directly impacts reimbursement negotiations with the National Association of Statutory Health Insurance Funds (GKV-SV). Products with limited clinical trial data, especially those for rare or life-threatening conditions, may require AbD to confirm their benefit-risk profile.

AbD procedures are regulated under Section 35a of SGB V and are initiated for specific products, such as those covered under Regulation (EC) No 726/2004 and Regulation (EC) No 141/2000. While AbD procedures can begin before approval, they are typically implemented post-market authorization and benefit assessment. Current experience indicates that some AbD procedures are triggered by urgent regulatory needs, while others are initiated post-assessment in response to new information or changes in conditions.

As the process continues to develop, timelines for the concept development, participation procedures, and data collection have been established, although precise timeframes are still evolving. Despite the complexity and the lengthy nature of AbD procedures, they play a vital role in ensuring that medicines with limited clinical trial data undergo thorough real-world evaluations. Initially launched in 2020 for individual cases, the number of AbD evaluations is steadily increasing, with the process continuing to adapt as more experience is gained.

10. Cost-effectiveness assessment of drugs according to Section 35b SGB V

This section outlines the purpose and process of cost-benefit assessment (Kosten-Nutzen-Bewertung, KNB) in Germany as defined in § 35b SGB V. The KNB is intended to provide an economic perspective to support AMNOG procedures, particularly during reimbursement negotiations.

A KNB can be requested either by the National Association of Statutory Health Insurance Funds (GKV-SV) or by the pharmaceutical company (pU), even in cases where the G-BA has not determined an added benefit. However, since the introduction of the AMNOG process in 2011, neither the statutory health insurers nor the pharmaceutical industry have initiated a KNB. Consequently, the IQWiG has not yet been commissioned by the G-BA to conduct such an assessment under § 35b SGB V.

Typically, a KNB includes the calculation of the incremental cost-effectiveness ratio (ICER) and a budget impact analysis. It does not provide an explicit price recommendation for medicinal products. Instead, it enhances transparency regarding cost-efficiency and offers a technical foundation for reimbursement decisions.

As the body commissioned by the G-BA, IQWiG is responsible for conducting the KNB according to international standards of evidence-based medicine and health economics. Recent methodological updates suggest that Germany is increasingly aligning itself with international norms in cost-effectiveness assessment. Since evolving methodology may pave the way for its future implementation, continued monitoring is recommended.

11. Impact of the German benefit assessment on reimbursement and pricing

This section discusses recent adjustments to Germany's drug pricing and reimbursement regulations, specifically within the context of the GKV-FinStG and the Medical Research Act 2025. It outlines the introduction of new pricing guardrails, including the calculation of price premiums or discounts based on the added benefit rating of medicines, and the impact of these regulations on price negotiations. The section details the implementation of a 20% combination discount for patent-protected drugs used in G-BA-designated combinations and the lowering of the annual revenue threshold for orphan drugs from €50 million to €30 million. It also highlights the introduction of the Medical Research Act, which aims to incentivize participation in clinical trials conducted in Germany by offering flexibility in reimbursement negotiations for drugs with substantial German patient involvement. The section concludes with recommendations for pharmaceutical companies, emphasizing the importance of aligning clinical trials with AMNOG requirements to avoid restrictions on negotiation flexibility, and the need to increase German patient participation in global clinical trials to overcome regulatory challenges.

Authors

List of authors in alphabetical order:

BÖHME, Sarah, Pfizer Pharma GmbH, Germany

BAUER, Robert, Novo Nordisk A/S, Denmark

GENET, Astrid, Pfizer Pharma GmbH, Germany

GRÖBNER, Monika, MSD Sharp & Dohme GmbH, Germany

HÄNSEL, Ivonne, Pfizer Pharma GmbH, Germany

HÖHNE, Anna, Pfizer Pharma GmbH, Germany

HUSCHENS, Susanne, Janssen-Cilag GmbH, Germany

KUCKA, Annett, SERVIER Forschung und Pharma-Entwicklung GmbH, Germany

KÜRSCHNER, Niclas, Pfizer Pharma GmbH, Germany

MARX, Almuth, Novartis Pharma GmbH, Germany

SCHLICHTING, Michael, Healthcare Business of Merck KGaA, Darmstadt, Germany

STERNBERG, Kati, AbbVie Deutschland GmbH & Co. KG, Germany

Authors contributed to different sections of the manuscript (authors in alphabetical order):

1. Overview and challenges of EU-HTA with a focus on German benefit assessment

Authors: *Sarah BÖHME, Monika GRÖBNER, Anna HÖHNE, Susanne HUSCHENS, Niclas KÜRSCHNER, Kati STERNBERG*

2. Appropriate comparator therapy

Authors: *Ivonne HÄNSEL, Anna HÖHNE, Annett KUCKA*

3. Pre-specified Analyses

Authors: *Astrid GENET, Annett KUCKA, Kati STERNBERG*

4. Actuality of data cuts in German HTA

Authors: *Annett KUCKA, Kati STERNBERG*

5. Patient-reported outcomes

Authors: *Robert BAUER, Monika GRÖBNER, Susanne HUSCHENS, Annett KUCKA, Niclas KÜRSCHNER, Almuth MARX, Michael SCHLICHTING*

6. Meta-analysis in the German benefit assessment

Authors: *Sarah BÖHME, Annett KUCKA*

7. Quantification of an added benefit without Head-to-Head Data – Historical comparisions

***Authors**: Astrid GENET, Annett KUCKA*

8. Definition and validation of Surrogate Endpoints

***Authors:** Robert BAUER, Sarah BÖHME*

9. Routine Practice Data Collection for the use of new pharmaceuticals

***Authors:** Susanne HUSCHENS, Annett KUCKA*

10. Cost-effectiveness assessment of drugs according to Section 35b SGB V

***Author:** Annett KUCKA*

11. Impact of the German benefit assessment on reimbursement and pricing

***Authors:** Susanne HUSCHENS, Almuth MARX, Kati STERNBERG*

Corresponding Author:

KUCKA, Annett, SERVIER Forschung und Pharma-Entwicklung GmbH, Germany

At this point, special thanks should be given to Friedhelm Leverkus for his support and helpful comments during the review process.

Acronyms and Abbreviations

AbD	Routine Practice Data Collection
ACT	Appropriate comparator therapy
AE	Adverse events
AESI	AEs of Special Interest
AMNOG	German Medicines Market Reorganization Act
ANCOVA	Analysis of covariance
ATE	Average treatment effect
ATMP	Advanced therapy medicinal products
ATT	Average treatment effect in the treated
ATU	Average treatment effect in the untreated
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CG	Coordination group
CHMP	Committee for Medicinal Products for Human Use
CIF	Cumulative incidence function
CSR	Clinical Study Report
EC	European Commission
EMA	European Medicines Agency
EU-HTA	European Union-Health Technology Assessments
FAS	Full Analysis Set
G-BA	German Federal Joint Committee
GKV-FinStG	German statutory health insurance policies-Financial Stabilization Act
HR	Hazard Ratio
HTA	Health Technology Assessment
HTAR	Regulation on HTA
HTD	Health Technology Developer
IPD	Individual patient data
IQWiG	Institute for Quality and Efficiency in Healthcare
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
JCA	Joint clinical assessment
LOCF	Last Observation Carried Forward
M(C)ID	Minimal (clinically) important differences
MAA	Marketing Authorization Application
MAR	Missing at random
MCAR	Missing completely at random
MFG	Medical Research Act
MMRM	Mixed model for repeated measures
MNAR	Missing not at random assumption
NRI	Net reclassification improvement
OS	Overall survival
PEI	Paul Ehrlich Institut
PRO	Patient-Reported Outcomes
PROM	Patient-Reported Outcome Measure
PS	Propensity score
PT	Preferred Terms
RCT	Randomized controlled trials
RR	Risk Ratio
SAP	Statistical Analysis Plan

SAS	Safety Analysis Set
SHI	Statutory Health Insurance
SOC	System Organ Class
STE	Surrogate threshold effect
SV	Surrogate validations
TTE	Time-to-event

Introduction

AMNOG and HTA Benefit Assessment of Drugs in Germany

The AMNOG (German Medicines Market Reorganization Act) process consists of two key steps: benefit assessment and price negotiation, both of which are highly regulated:

1. Benefit Assessment – The German HTA Process

When a pharmaceutical company introduces a new drug with a new active ingredient in Germany, it must demonstrate the drug's added benefit. The same applies, if the drug receives a marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 number 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008.

The process typically takes six months. The G-BA (German Federal Joint Committee), the highest decision-making body overseeing the self-governance of physicians, dentists, psychotherapists, hospitals, and health insurance funds in Germany, determines the required evidence for each drug.

The G-BA specifies the appropriate comparator therapy (ACT) and the endpoints to assess the added benefit of the drug. The AMNOG dossier, prepared by the health technology developer (HTD), is first assessed by IQWiG (Institute for Quality and Efficiency in Health Care) or G-BA. Based on this evaluation, the G-BA decides on the added benefit of the drug.

2. Price Negotiation

The results of the benefit assessment guide the subsequent price negotiation process. Pharmaceutical companies and the GKV-SV (National Association of Statutory Health Insurance Funds) negotiate the reimbursement amount, which should reflect the "value" of the drug.

In May 2017, the German legislator introduced changes to the regulations governing price negotiations with the Act to Strengthen the Supply of Medicines in the Statutory Health Insurance (AMVSG (Bundesanzeiger, 2017). This amendment aimed to provide more flexibility in pricing, especially for new patent-protected drugs with unproven additional benefit. Under the previous law, these drugs could not lead to higher annual therapy costs than the most cost-efficient ACT set by the G-BA. The new regulation, however, softened the language from “must not” to “shall not,” allowing for deviations from the cost cap in justified cases (Bundesanzeiger, 2016), (Bundesanzeiger, 2017).

Focus of the German Benefit Assessment White Paper

The German Benefit Assessment White Paper focuses on the current methodological requirements of the German HTA process, emphasizing its importance not only in assessing drug benefits but also in determining drug pricing.

1. Overview and challenges of EU-HTA with a focus on German benefit assessment

Authors: Sarah BÖHME, Monika GRÖBNER, Anna HÖHNE, Susanne HUSCHENS, Niclas KÜRSCHNER, Kati STERNBERG

1.1 Abstract

This section outlines the introduction and impact of the European Joint Clinical Assessment (JCA) under Regulation (EU) 2021/2282, which aims to enhance patient access to innovative health technologies and reduce duplication of efforts in Health Technology Assessments (HTA) across the EU. Starting in 2025, new medicines, including oncology and Advanced Therapy Medicinal Products (ATMPs), will undergo clinical assessments at the European level, with orphan drugs assessed by 2028 and all other medicines by 2030. Despite this harmonization, national HTA authorities will still perform complementary evaluations. For Germany, the JCA report, though crucial, may not be available by the time the national dossier is submitted. Therefore, and due to potential additional evidence requests the creation of a "delta dossier" to address any missing information might be neccessary. The timelines for JCA are aligned with the EMA process, and the German benefit assessment will incorporate both the national and JCA dossiers. The section discusses the current developments and uncertainties in the system as it adapts to the new EU regulations, recommending close collaboration between the HTD and national AMNOG teams to ensure alignment with German PICO requirements. As the system evolves, ongoing monitoring and adaptation are essential to address emerging challenges.

1.2 Introduction

In addition to HTA processes at national level, a Joint Clinical Assessment (JCA) for new medicines has been introduced at European level. Regulation (EU) 2021/2282 on Health Technology Assessment (EU-HTAR) contributes to improving the availability of innovative health technologies, such as medicines and certain medical devices, to EU patients (EUR-Lex, 2021). It ensures an efficient use of resources and strengthens the quality of HTA across the Union (European Commission, 2021).

This HTAR entered into force in January 2022 and applies to new submissions to the EMA from 12 January 2025. From 12 January 2025, new active substances for the treatment of cancer and medicines regulated as ATMPs will be clinically assessed at European level. Orphan drugs will be assessed by a European JCA by 2028 and all other medicines by 2030. However, conclusions on benefit or added clinical value and pricing will remain at national level. The objectives of EU-HTAR are specifically to:

- reduce duplication of efforts for national HTA authorities and industry
- improve patient access equity
- strengthen the quality of clinical assessments
- strengthen the pharmaceutical sector in Europe and its international competitiveness.

The assessment scope for JCA should be inclusive and should reflect all Member States' needs in terms of data and analyses to be submitted by the health technology developer. The assessment scope should include all relevant parameters in terms of the PICO scheme:

- **P**atient population
- **I**ntervention
- **C**omparator(s)
- **O**utcomes.

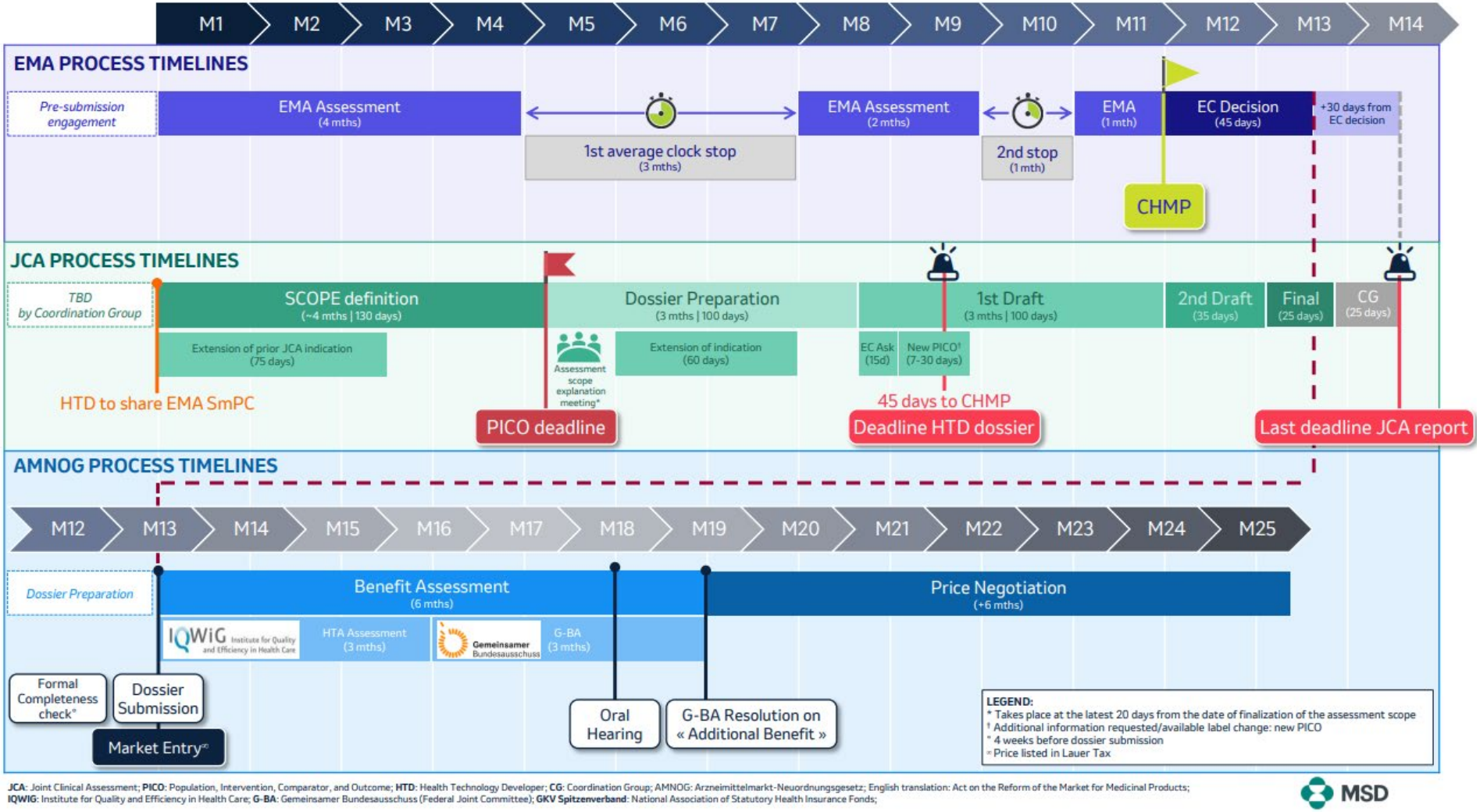
Despite efforts to harmonize the assessment scope at the EU level, Member States will still be able to perform complementary clinical evaluations, when necessary. This applies for patient groups, comparators or health outcomes, as well as using a different methodology than in the JCA. With the Regulation stating, that no duplication of work is permitted, for Germany there will be a German document that only includes references to pertinent parts of the European submission as well es complementary analyses to the JCA report, often referred to “delta dossier”.

1.3 Timelines

The timelines of the JCA are strictly aligned to the marketing authorization/EMA process (see Figure 1: Timelines of the JCA to the EMA authorization process). Therefore, the timepoints are defined in days from start of the EMA process.

After receipt of a marketing authorization application (MAA), the HTA secretariat is informed about the process and receives relevant information by the HTD. The JCA process starts with the scoping phase. During that time the JCA subgroup harmonizes the PICOs of the member states. For new medicinal products, the JCA subgroup shares the requested PICOs with the HTD at day 130 after start of the EMA process and offers an assessment scope explanation meeting. So far, this seems to be the only timepoint where an exchange between JCA subgroup and HTD is planned. The work for the HTD on the JCA dossier preparation is running in parallel to answering the questions during the first clock stop in the EMA process. There are 100 days only, in case of a first assessment, to write the JCA dossier for all PICOs requested, so effectively the HTD must start its work much earlier. The submission deadline for the JCA dossier is 45 days prior to CHMP opinion the latest. The JCA subgroup drafts a JCA report until 30 days following adoption of EC decision (+10 working days of procedural check by EC). During that phase, the HTD is given the opportunity of a fact check, but no interaction on the content is planned.

Figure 1: Timelines of the JCA to the EMA authorization process



JCA: Joint Clinical Assessment; **PICO**: Population, Intervention, Comparator, and Outcome; **HTD**: Health Technology Developer; **CG**: Coordination Group; AMNOG: Arzneimittelmarkt-Neuordnungsgesetz; English translation: Act on the Reform of the Market for Medicinal Products; **IQWIG**: Institute for Quality and Efficiency in Health Care; **G-BA**: Gemeinsamer Bundesausschuss (Federal Joint Committee); **GKV Spitzenverband**: National Association of Statutory Health Insurance Fonds;

For the extension of an indication, EMA timelines as well as JCA timelines are extremely shortened and require close collaboration of all involved parties.

For the German benefit assessment, the national dossier must be submitted in a final version as soon as the new medicinal product enters the German market or, in the case of extended indications, within 4 weeks after EC decision. The G-BA considers the national and the JCA dossier as well as the JCA report in its benefit assessment.

1.4 Relevance of the JCA report for German benefit assessment

The JCA report may not be available at the timepoint of submission of the national dossier to G-BA. For that reason, the G-BA considers also the JCA and the national dossier, besides the JCA report, as sources for its benefit assessment.

Ideally, the German PICO should be completely represented in the JCA dossier, without any population splitting, so that the evidence from the JCA report can be transferred. However, it is unclear how German implicit requirements will be part of the PICO (e.g. level of detail of adverse event analyses, accepted PRO scales or subgroup analyses) and how to deal with details that are not part of the PICO and hence the JCA report. Therefore, any missing information must be presented in the national HTA dossier ("delta dossier"), keeping in mind that no duplication is permitted.

The EU-HTA guidelines show a relatively large overlap with IQWiG methodology and G-BA requirements. If there are any deviations from the German methodology or additional analysis have been agreed to support the value proposal, appropriate additions should be made to the German benefit dossier.

With the start of EU HTA on January 12th, 2025, only preliminary adaptions in the German procedure have been published by the ministry of health and G-BA. Such is still unclear what the German process of requesting additional information (as a supplement to the EU-HTA dossier) will look like in practice. However, the procedural harmonization between EU-HTA and German HTA will be implemented stepwise.

1.5 Current development

Just before the start of the EU-HTA, all implementing acts and relevant guidance documents for medicinal products were published. However, the German system still needs to adapt to the new regulation, for instance, by releasing updated dossier templates that accommodate "delta dossiers." It is still unclear if and to what extent the G-BA will adjust its requirements under AMNOG. All new medicinal products (oncology and ATMPs) applying for marketing authorization at EMA for the first time will now undergo the JCA. Despite progress, there remains considerable uncertainty at both the EU and national levels. As more experience is accumulated, continuous changes and adjustments are expected. During this learning phase of the system, close monitoring should be maintained to ensure timely responses to these adaptations.

1.6 Recommendation

Ideally, the German PICO should be completely represented in the JCA dossier. For Germany, a G-BA advice meeting is possible during the development of a phase 3 study protocol as well as prior to launch and should be used to predict the German PICO. A very close collaboration internally is needed to meet the requirements and timelines. The HTD's German AMNOG dossier team must be

involved in strategic plans for the JCA dossier to react with their national AMNOG dossier strategy. As IQWiG was the leading party during the development of the JCA methodology, a lot of JCA methodological requirements are similar to AMNOG requirements, a close collaboration is even more desirable.

2. Appropriate comparator therapy

Authors: Ivonne HÄNSEL, Anna HÖHNE, Annett KUCKA

2.1 Abstract

This section discusses the process of determining the Appropriate Comparator Therapy (ACT) within the German healthcare system, as outlined by the G-BA (Gemeinsamer Bundesausschuss). The ACT is used as the standard comparator for evaluating new treatments and is essential for the benefit assessment process. Key criteria for determining the ACT include marketing authorization for the relevant indication, reimbursement by Statutory Health Insurance (SHI), previous G-BA resolutions, and alignment with the current medical standard. The ACT may change throughout the benefit assessment process, such as after early consultations, during ongoing studies, or after the submission of the benefit dossier. Various factors, including new scientific evidence and regulatory changes, can trigger modifications to the ACT. This section emphasizes the importance of staying informed and prepared for potential ACT changes to mitigate risks, offering strategies for pharmaceutical companies, including proactive monitoring of evidence, early engagement for study design, and ongoing adjustments to strategies. Additionally, the evolving landscape of the EU Health Technology Assessment (EU-HTA) is discussed, highlighting the complexity of defining comparators across different member states.

2.2 Introduction

The determination of the ACT is carried out by the G-BA and represents the standard treatment in Germany. During advisory meetings, the G-BA can be asked how they derive the ACT for a specific indication and patient population.

Criteria for Determining the ACT (according to the G-BA Code of Procedure, Chapter 5 § 6):

- **Marketing Authorization:** A medicinal product used as a comparator must generally have marketing authorization for the indicated condition.
  Note: In exceptional cases a product can be considered an ACT even if the indication is not covered by its authorization.
- **Reimbursable by Statutory Health Insurance (SHI):** Non-drug treatments considered as comparators must be available within the framework of statutory health insurance.
- **G-BA Resolution:** Products or treatments whose added benefit has already been determined by the G-BA should preferably be used as comparators.
- **Medical Standard:** Comparator therapies should align with the generally recognized state of medical knowledge in the relevant therapeutic area.

In an ideal scenario, clinical trials for benefit assessment are designed under consideration of the G-BA-determined ACT, and RCT data are presented in the benefit dossier demonstrating the added benefit over the ACT.

In G-BA consultations, one can inquire about the current derivation of the ACT. However, this consultation is not binding. The ACT can change at any time during the procedure. The ACT that is actually used to derive the added benefit is only found in the G-BA decision.

2.3 Timepoints of ACT changes

Changes to the ACT may occur at various stages, as illustrated in Figure 2:

- Following a (early) G-BA advice
- During an ongoing study (with potential multiple adjustments)
- Just before dossier submission
- After dossier submission, during the ongoing assessment
- After the written statement process at the G-BA
- Upon the G-BA's decision on the added benefit (potentially triggering a follow-up procedure)

The legally binding determination of the appropriate comparator therapy occurs at the time of, or with, the benefit assessment decision.

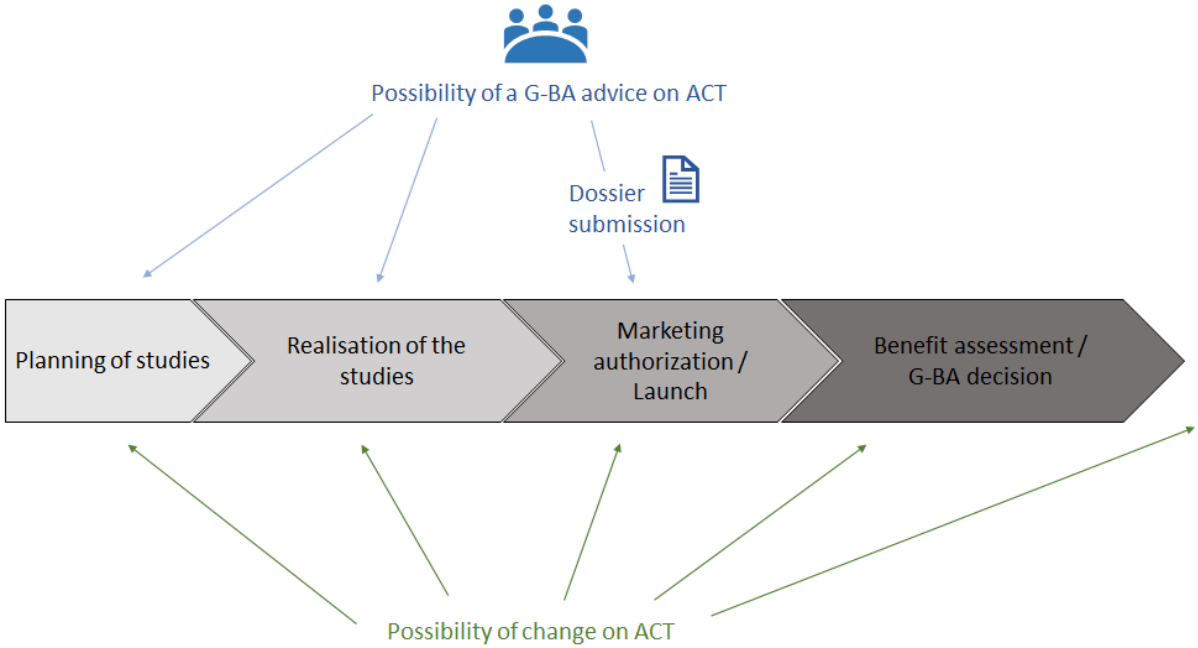


Figure 2: Advice on and amendment of the ACT in the German benefit assessment

There is currently no recognizable system that can predict when or if ACT changes will occur. Therefore, this guidance aims to help assess risks and determine the necessary precautions in case an ACT change takes place.

ACT changes can be triggered by various factors, such as new scientific findings, updates in regulatory assessments, or changes in the manufacturing process of substances. Common reasons include:

- Changes to medical guidelines or the introduction of new medical standards
- Label changes during the regulatory procedure
- New G-BA resolutions for competitor products, which influence the ACT depending on the extent of the added benefit.

Therefore, it is crucial to regularly check for the most current information and be prepared for potential ACT changes in order to minimize risks. The types of ACT, with descriptive examples, are

outlined in the Appendix, including the impact of an ACT change within a procedure. The appendix also details which indication areas are frequently affected and lists the most common reasons for ACT changes.

2.4 Current development: EU HTA

Under ideal circumstances, the comparator for an EU-wide acceptable clinical trial for benefit assessment would be:

- The reference treatment, as outlined in high-quality clinical practice guidelines at the European or international level.
- A treatment with EU or national marketing authorization for the relevant indication and line of treatment.

Guidance to ensure consistent definitions for different comparators can be found in the "Guidance on the scoping process". Clinical trials with multiple comparators may be required to meet the diverse needs of member states, but this makes the statistical analysis of the results more challenging.

Additionally, changes in the label during the regulatory process could lead to modifications in the acceptable comparator treatment.

2.5 Recommendation

Strategies for Pharmaceutical Companies to Address Potential ACT Changes

1. Proactive Surveillance and Information Monitoring
   - Continuously track and analyze updated evidence and literature to stay ahead of potential ACT changes.
   - Regularly review benefit assessments of comparators to ensure alignment with evolving standards.
   - Stay informed on medical guidelines and treatment standards to anticipate shifts in clinical practices.
2. Early Engagement for Study Design
   - Seek early-stage advice to design Phase 3 studies that are tailored for benefit assessment processes.
   - Ensure study designs account for potential ACT modifications, such as:
     - Including multiple comparators or arms.
     - Planning for indirect treatment comparisons when applicable.
3. Ongoing Strategy Adjustment
   - Revisit and update early advice when preparing the benefit dossier, ensuring that the latest information is incorporated.
   - Continuously monitor updates in treatment guidelines and competitor activities, including new authorizations and G-BA resolutions.

3. Pre-specified Analyses

Authors: Astrid GENET, Annett KUCKA, Kati STERNBERG

3.1 Abstract

This section focuses on the importance of pre-specification in benefit assessments under the AMNOG (German Act on the Reform of the Market for Medicinal Products) process, emphasizing the distinction between pre-specified analyses and post-hoc analyses in clinical trials. Pre-specification, outlined in the study protocol or Statistical Analysis Plan (SAP), is crucial for maintaining transparency and integrity in clinical data analysis. Key components of HTA (Health Technology Assessment) under AMNOG include the study population, subgroup analysis, endpoints, safety analysis, and statistical methodologies. The G-BA's requirements guide the structure of analyses, such as focusing on patient-relevant outcomes and using relative risk (RR) or hazard ratios (HR) for effect size estimation. The section also discusses the implications of the evolving EU-HTA framework, which may lead to adjustments in analysis methods, particularly with indirect comparisons and single-arm trials. Recommendations are provided for optimizing pre-specification and aligning with G-BA requirements, emphasizing early planning, adherence to pre-specified analyses, and proactive G-BA engagement to ensure a successful benefit assessment process.

3.2 Introduction

In benefit assessments under AMNOG, pre-specification is key to maintaining the integrity and transparency of clinical trial data analyses. It is important to distinguish between pre-specification—outlined in the study protocol or SAP—and post-hoc analysis, which refers to any analysis performed after the trial data are available. Pre-specification must occur prior to the first data cut and, for blinded studies, specifically before the unblinding of data.

Benefit assessments require specific analyses mandated by IQWiG/G-BA, including those requested during G-BA consultations, benefit assessments, or oral hearings. Additionally, analyses prescribed by methods papers or templates must be addressed. According to IQWiG's General Methods, complementary analyses specified by HTA authorities, such as subgroup analyses, should not be considered "post hoc" in the context of a systematic review. Instead, these analyses represent hypotheses to be tested during the review" (IQWiG, 2023).

3.3 Key components of HTA-assessments

Early consideration of the dossier-relevant questions in the design of the clinical trial program is the simplest key to a positive benefit assessment. In most cases, however, study design elements and analyses must be pre-specified in a study protocol or a separate SAP. As usual in planning of statistical analysis, it is important that this is planned sufficiently early to avoid a data-driven analysis.

The requirements for a pre-specified data analysis as part of the benefit assessment are discussed below.

Study Population and Analysis sets

Unless otherwise required by the G-BA, the entire study population should be analyzed. However, the focus may be narrowed to a subpopulation (e.g., label-compliant population), which would then be analyzed based-on characteristics collected prior to randomization or prior to treatment of a patient. Since these analyses are defined by the G-BA, they should not be regarded as 'post hoc'. Regardless, all randomized patients, whether from the entire study population or the G-BA-required subpopulation, should be considered for HTA assessment. The analysis is conducted in the Full Analysis Set (FAS)/Intention-to-Treat (ITT) analysis set (SAS for safety), independently of the analysis set pre-defined in the SAP for the assessment of the primary endpoint(s). However, the pre-specified set is also accepted in case of minor deviations from FAS/ITT. For example, including only those patients who received treatment or those with at least one post-baseline visit, if it impacts only a small number of patients.

Subgroup Analysis

The submission template by G-BA specifies mandatory subgroups: age, gender, geographic region and disease severity. Independent of prespecification, these subgroups have to be included into the dossier.

In addition, subgroup analyses should be presented for the subgroups specified in the study protocol or SAP and for all specified randomisation factors, if available. It should be noted that subgroup analyses must performed for all G-BA-relevant endpoints even if the subgroup was only prespecified for a subset of endpoints e.g. the primary endpoint. In general, subgroup analyses are only performed if there are at least 10 patients in each category for a given subgroup, and at least 10 events in one of the categories for binary and time-to-event (TTE) data.

Subgroup analyses are required for the main analysis. Sensitivity and supportive analyses do not need to be broken down by subgroup.

Endpoints and Estimates

In the German benefit assessment, the inclusion of endpoints is determined solely by their acceptance by the G-BA, rather than their classification as primary, secondary, tertiary, or exploratory endpoints. For instance, only patient-relevant outcomes are considered in the German benefit assessment. These outcomes must reflect a treatment's ability to reduce disease- and symptom-related burdens that patients can directly experience.

Regarding the estimation of accepted endpoints, the G-BA primarily demands the use of relative risks (RR) or hazard ratios (HR), irrespective of the prespecified estimate. These measures are preferred to better evaluate the relevance of a treatment for patients. For non-binary patient-reported outcomes (PROs) or other non-binary efficacy outcomes, the use of a 15% scale range as a response threshold is proposed to estimate RR or HR, albeit controversially (Böhme, et al., 2021).

Additionally, mean differences in the form of the standardized mean difference (Hedges' g) are accepted for continuous outcomes. This metric allows for quantifying the effect size in a way that is comparable across various studies and measurement tools.

A special case arises when there are differences in observation duration between the treatment arms. In such instances, event-time analyses are required, independent of the prespecification, to accurately account for the impact of different observation periods and to ensure reliable results.

Safety endpoints

Comparative analysis should be reported for safety endpoints, even if pre-specified as descriptive only. Safety endpoints are analyzed as binary endpoints.

The analysis should be reported for the categories detailed below:

- Overall rates of adverse events (AEs)
- SOCs/PTs related to underlying disease progression should be excluded from safety analysis for the overall rates of adverse events.
- Any AE
- Serious AE
- Severe AE
- Temporary discontinuation from study drug or dose reduction due to AEs
- Discontinuations from study drug due to AE

AEs by System Organ Class (SOC) and Preferred Terms (PT):

- Any AE occurring in > 10 % of patients or >= 10 patients in at least one treatment arm
- Serious AE occurring in > 5 % of patients or >= 10 patients in at least one treatment arm
- Severe AE occurring in > 5 % of patients or >= 10 patients in at least one treatment arm
- Discontinuations from study drug due to AE

AEs of Special Interest (AESIs): AESIs pre-defined in the SAP or required by the G-BA (specific to an indication or a molecule) should be represented if they are not already covered by the representation at SOC/PT level, for instance if they are SMQs or other otherwise pre-specified events.

- Any AESI
- Serious AESI
- Severe AESI

Statistical analyses, models and imputation

Usually, the G-BA relies on the pre-specified statistical analyses methods, models and imputation methods. When the pre-specified estimate is not accepted by the G-BA, necessary deviations also in the statistical analyses must be adopted, and a new analysis for the accepted estimate should be utilized. In such cases, it is recommended that the new analyses method and statistical model should mirror the old one as closely as possible (e.g., stratification factors), wherever feasible.

Regarding imputation, the G-BA clearly favors the treatment policy approach. However, well-justified exceptions are accepted, though ideally, these exceptions should also be prespecified.

3.4 Current development and EU-HTA

The EU-HTA guidance on outcomes for Joint Clinical Assessments (JCA) (HTA CG, 2024) may prompt adjustments to the pre-specified analyses included in the HTA assessment. Specifically, the EU JCA approach places greater emphasis on indirect comparisons and single-arm trials, which could influence the scope and methodology of the analyses. Despite these potential shifts, most methodological aspects are expected to align with the current standards of the German AMNOG process (Kisser , et al., 2022). These guidelines will likely extend beyond the analyses presented in the Clinical Study Report (CSR) of the pivotal trial and those pre-defined in the Statistical Analysis Plan (SAP).

Notably, while the EU-HTA guidance offers a more flexible framework for indirect comparisons, it still requires rigorous and well-documented methods to ensure robust and reliable results. This may necessitate the inclusion of additional data or statistical models that were not originally anticipated in the SAP. Furthermore, the evolving nature of HTA methods in the EU context may lead to the incorporation of new analytical approaches or a more refined focus on patient-relevant outcomes, aligning with ongoing efforts to improve transparency, consistency, and comparability in benefit assessments across member states.

3.5 Recommendation

Based on the key points discussed, the following recommendations are made to optimize pre-specification and analysis within the context of AMNOG assessments:

1. **Early Pre-specification:** Ensure all critical analyses are pre-specified in the study protocol or SAP before the first data cut and before unblinding in blinded studies.
2. **Adapt to G-BA Requirements:** Recognize that specific requirements from the G-BA should not be treated as post-hoc.
3. **Adhere to Pre-specified Analyses:** Use pre-specified analyses as outlined in the SAP, unless the G-BA mandates otherwise. Any deviations should be thoroughly justified.
4. **Seek G-BA Guidance:** Proactively consult with the G-BA to ensure alignment between the study design, statistical analyses, and regulatory expectations. Address any concerns early in the process to avoid delays.

4. Actuality of data cuts in German HTA

Authors: Annett KUCKA, Kati STERNBERG

4.1 Abstract

This section discusses the role and requirements of data cuts in the German benefit assessment process under AMNOG (German Act on the Reform of the Market for Medicinal Products). A data cut refers to a point in time when clinical trial data is considered sufficient for analysis to answer the study objectives. The section distinguishes data cuts from other types of analyses, such as blinded or interim analyses. It emphasizes the need for a benefit assessment dossier to describe all planned data cuts, including those requested by regulatory authorities, and to provide clear justifications for any excluded or non-relevant data cuts. The focus of the G-BA (Federal Joint Committee) is on the most mature data cut, with incomplete or outdated data cuts potentially affecting the perceived completeness of the submission. The submission of data cuts up to three months prior to dossier submission is mandatory, and later submissions may be possible as part of a written statement. The section also highlights the importance of aligning regulatory and HTA data to minimize inconsistencies and ensure comprehensive, reliable data. It provides recommendations for managing and presenting data cuts to optimize the benefit assessment process, ensuring a high-quality dossier that supports better decision-making.

4.2 Introduction

A data cut in clinical trials refers to a specific point in time when data is considered sufficient for analysis to answer study objectives. This involves capturing all available data up to a predetermined date or event, ensuring that the dataset is complete and consistent for the purposes of interim or final analysis. In the context of AMNOG, data cuts should be distinguished from data snapshots involving any kind of blinded analyses only, analyses only for a Data Monitoring Committee (DMC), or futility analyses.

A benefit assessment dossier should describe whether and for what reason different data cuts were conducted or are still planned. It should also be stated whether these data cuts were planned in advance (i.e. in the statistical analysis plan (SAP)). As a rule, only the presentation of data cuts planned a priori or requested by the regulatory authorities is required.

The aforementioned data cuts should be carried out and presented in full, i.e. for all relevant endpoints collected. This also applies if a data cut was originally only planned to analyse individual endpoints. The focus of the G-BA generally lies on the latest, most mature data cut. The presentation of the results of individual endpoints of a data cut-off or an entire data cut-off may be omitted if this is not expected to result in a significant gain in information compared to another data cut-off (e.g. if the follow-up for an endpoint was already almost complete for the previous data cut-off or if a data cut-off is in close temporal proximity to another data cut-off) (IQWiG, 2023).

The submission of non-relevant data cuts can be waived with justification if no additional knowledge is gained. However, the decision on the relevance of the data cut-off lies with G-BA.

4.3 Requirements

The requirement to present all planned data cuts, including those requested by regulatory authorities, often results in a significant workload due to repetitive information. While non-relevant data can typically be omitted, the G-BA decides on this matter during the review process, often relying on the initially submitted data. Subsequent submissions of data—whether because a data cut was unavailable at the time of submission or because the G-BA determines it to be relevant—are possible as part of the written statement. However, they are generally not preferred, as this can lead to data gaps for discussion during oral hearings. Last-minute data submissions may not be reviewed at that point, which could require re-evaluations and increase workload.

It is important to note that deviating from presenting all required data cuts or omitting the most current one does not automatically result in data rejection. Valid reasons may exist for excluding certain endpoints or using older data, but this can affect the acceptance and perceived completeness of the data. While there are few precedents outlining the consequences of such deviations, decisions regarding the timeliness of data cuts in benefit assessments should be grounded in a solid scientific foundation to ensure the quality and reliability of evaluations.

Moreover, data used for regulatory decisions may not always be suitable for HTA (Health Technology Assessment) purposes. Specifically, the data used for risk-benefit assessment in the marketing authorization process may differ from those needed for HTA benefit assessments, increasing the potential for incongruent analysis results.

Up-to-date data cuts are also vital in the regulatory process, particularly for improving the accuracy of safety estimates. Inconsistencies may arise due to the different data cuts used in the approval and benefit assessment processes, especially given the temporal gap between the two processes. These inconsistencies can be further exacerbated by the fact that regulatory bodies often have different evaluation criteria.

An additional key aspect of the timeliness of data cuts in the German benefit assessment process is the requirement for completeness. It is crucial to ensure that the data cut is comprehensive and free from errors, such as using partially cleaned data, to avoid issues during the evaluation. This should be carefully considered during study planning to ensure high-quality data submission.

4.4 Methodology

All data cuts must be submitted in complete form, i.e. for all endpoints. This also applies in particular to interim analyses, even if these were only pre-specified / carried out for selected endpoints.

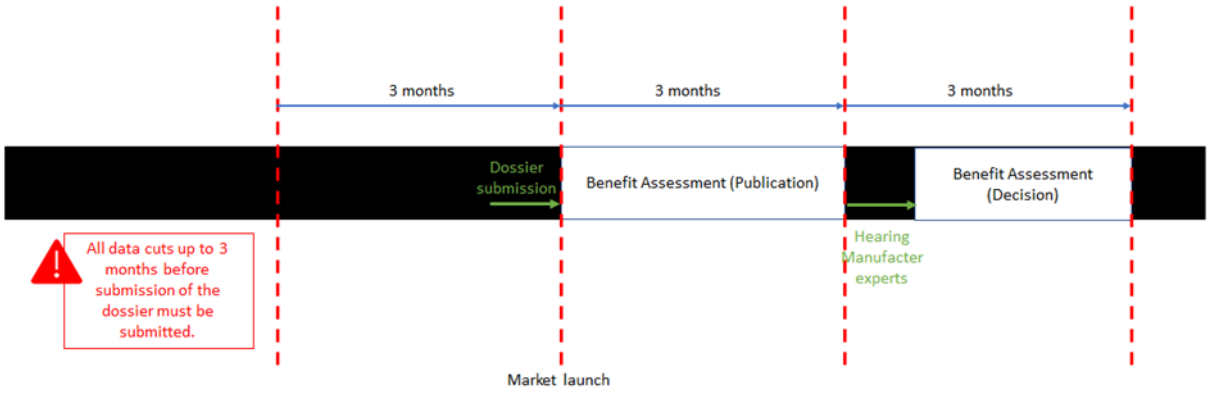


Figure 3: Timelines of the submission of data cuts

All data cuts up to 3 months before submission of the dossier must be submitted. Subsequent submission within the written statement is also possible (e.g. the data section was not yet available at the time prior to dossier submission and could therefore not be included in the dossier) (see Figure 3).

Some examples of the submission of data cuts in the German benefit assessment can be found in the appendix of the document (see Appendix for Chapter 5. Actuality of data cuts in German HTA – Examples).

4.5 Current development

Due to the time frame, different or more recent data cuts may be relevant for the German HTA dossier compared to the data cuts submitted in the marketing authorization or EU-HTA. Therefore, it is very likely that additional data cuts will need to be analyzed for the dossier in order to obtain more mature and valid data.

Such a data cut could include, for example, a 4-month safety update or a data cut requested by the regulatory authorities (FDA or EMA).

Furthermore, a relevant data cut in the German HTA process requires that it has been pre-planned (e.g., in the statistical analysis plan) and provides an information gain. It should be noted that a more recent data cut with an information gain may also enable a new assessment at the EU-HTA level.

4.6 Recommendation

In the German benefit assessment process, the quality and timing of data cuts are crucial. Proper management and presentation can significantly influence the G-BA's evaluation. Here are the recommendations to optimize this process and align with regulatory and HTA requirements:

- Balance the focus on the essential and most important data against the presentation of all a priori planned or regulatory-requested data cuts up to three months before dossier submission. Clearly justify the exclusion of non-relevant data cuts to ensure emphasis on the most critical information. The G-BA will make the final decision on the relevance of the excluded data cuts.
- Ensure all relevant data cuts, including interim analyses, are pre-planned in the Statistical Analysis Plan or the Study Protocol.

- Submit up-to-date and complete data cuts and avoid last-minute updates. Plan studies to avoid partially cleaned data.
- Align data sets for regulatory approval and HTA to minimize inconsistencies. Utilize recent data cuts that provide significant information gain.

By following these guidelines, the quality and reliability of AMNOG dossiers will improve, thereby supporting better benefit assessment decisions.

5. Patient-reported outcomes

Authors: Robert BAUER, Monika GRÖBNER, Susanne HUSCHENS, Annett KUCKA, Niclas KÜRSCHNER, Almuth MARX, Michael SCHLICHTING

5.1 Abstract

This section outlines the requirements and considerations for Patient-Reported Outcomes (PROs) in the German Health Technology Assessment (HTA) process, highlighting their critical role in establishing the added benefit of new treatments. PROs, particularly those measuring Health-Related Quality of Life (HRQoL), are essential for assessing treatment impact, as they directly reflect patients' health status and symptoms. The G-BA mandates the inclusion of HRQoL data in benefit assessments, and the absence of such data is often criticized. The section covers the use of psychometrically validated instruments, estimand considerations for analyzing PRO data, and the importance of data quality and completeness. A treatment policy estimand is recommended to handle intercurrent events, such as treatment discontinuation or disease progression. The analysis also addresses challenges in handling missing data and the use of responder analyses based on Minimum Important Differences (MID). The section discusses the clinical relevance of MIDs, the use of Hedges' g for continuous data, and the role of indirect treatment comparisons (ITCs) for PROs. Current developments in the EU HTA process are also reviewed, emphasizing the need for harmonization between national and European approaches. Recommendations focus on aligning PRO assessment methods to ensure consistency, reduce redundancy, and enhance the transferability of HTA evaluations across both national and European contexts.

5.2 Introduction

In the German HTA process, an added benefit of an intervention can only be established based on patient-relevant endpoints, including mortality, morbidity, HRQoL, and safety. PROs are crucial as they can directly measure health status (e.g. symptoms), functioning, and HRQoL from the patient's perspective. PRO-based HRQoL measures are particularly important for benefit assessment. For example, without HRQoL data, interpreting the impact of adverse events (AEs) can be challenging, especially when comparative safety assessments highlight risks. In some therapeutic contexts, an overall survival (OS) benefit alone may not be sufficient to demonstrate additional benefit if AEs cause harm or worsen quality of life. The G-BA requires HRQoL data to assess the overall impact of a new treatment. The lack of HRQoL data in pivotal trials is regularly criticised by the G-BA, as it negatively affects the outcome of the benefit assessment.

5.3 PRO assessment requirements

Psychometrically validated instruments, preferably using a disease specific and a generic instrument. Core aspects of the required psychometric measurement properties include

- Reliability,
- Validity,
- Ability to detect change,
- Interpretability,
- Acceptability and

- Appropriateness.

It is important to note that validation studies must be referenced and checked if they still fit the purpose. For instance, a validation study conducted in breast cancer patients may lack sufficient evidence for ovarian cancer patients e.g. to detect a meaningful change. There are several ways to assess these measurement properties, and regulatory agencies such as the EMA and FDA have published guidance on this (Böhme, et al., 2021).

It should be noted that utility measures, such as those derived from EQ-5D or SF-6D instruments to calculate quality-adjusted life years, play a limited role in the current German HTA process (in contrast the EQ-5D VAS is typically seen as patient-relevant).

5.4 Estimand considerations

In general, the choice of a PRO estimand depends on the research question and the related clinical study objectives. Different estimands may lead to different conclusions and implications for clinical practice (IQWiG, 2023). The PRO objectives of the registrational trial may support a while-on treatment or while-alive intercurrent event strategy. However, for German benefit assessment, IQWiG's General Methods describe the treatment policy estimand strategy as the relevant strategy for dealing with intercurrent events (e.g. events of discontinuation or change of treatment, use of concomitant medication (e.g. painkillers), disease progression, etc.). This means that the research objectives seek to understand the treatment effect on the PRO endpoint independent of the intercurrent event (i.e. the values observed for the endpoint are relevant to the analysis whether or not the intercurrent event (ICE) occurs (Lawrance, et al., 2020). An important implication for the study design is that PRO instruments need to be collected independently of the occurrence of intercurrent events. IQWiG's General Methods state that "...data on all outcomes relevant to the assessment, including PROs and adverse events, should be collected completely, even after discontinuation or switching of treatment". This could impact in particular the design of pivotal oncology studies where such data is collected to answer PRO research questions for regulatory purposes which might limit the data collection to the period up to disease progression.

Of note, death is a terminal event and post-event observations cannot be expected. Currently, death has not been treated differently from other unobserved values based on ICEs, and thus the common practice is to consider a hypothetical strategy or a composite strategy. Alternatively, a 'while alive' strategy could be relevant in certain settings (e.g. palliative care).

5.5 Data quality and completeness

Similar to regulatory requirements such as ICH E9, HTA emphasizes the inclusion of all randomized patients in the statistical analysis. IQWiG requires a treatment effect estimate for the entire treatment strategy, regardless of intercurrent events (e.g. treatment discontinuation, patient withdrawal, disease progression, or treatment changes), based on the intention-to-treat principle (IQWiG, 2023). Therefore, missing data for the primary estimation are critical. According to the treatment policy estimate, data are considered missing if they are not observed according to the study protocol. As a result, PRO return rates should include all randomized/treatment patients in the denominator. Excluding deceased patients or those for whom PROs are not expected from the denominator after death has been accepted in the past and provides valuable information on data quality and completeness.

In Germany, specific thresholds define what constitutes a substantial amount of missing data. PRO data are generally excluded from benefit assessments if more than 30% of participants are not included in the analysis. Additionally, if the difference in the proportions of participants excluded between groups exceeds 15 percentage points, this suggests non-random exclusion, and the results are not considered in the benefit assessment (IQWiG, 2023). Such a scenario would favor a missing-not-at-random (MNAR) assumption.

The impact of missing data depends on the statistical analysis method. For instance, in a mixed model for repeated measurements (MMRM) analyzing change from baseline, the relevant return rates include all patients with a valid baseline and at least one non-missing post-baseline measurement. The same applies to time-to-first-deterioration or other time-to-event analyses. However, for binary analyses at specific time points (e.g., responders at week 52, with a baseline-to-week-52 change exceeding a cutoff), the return rates only consider patients with valid baseline and week 52 data. If PRO returns decline significantly throughout the study, models like MMRM, which consider all time points simultaneously, may increase the relevant return rates.

In the dossier, return rates for each time point and the number and percentage of patients included in the analysis must be reported.

5.6 Analysis

5.6.1 Analysis requirements

In principle, when both analysis of continuous data and also suitable responder analyses based on a minimally important difference (MID, response criterion pre-specified at least 15% of the scale range or exactly 15% of the scale range post hoc) are available, then the responder analyses are used.

For time-to-event responder analyses (event can be a deterioration and/or an improvement) based on MIDs, the G-BA mentions the following options:

- **Time to first change:** The response threshold is exceeded only once. Subsequent assessments are not relevant.
- **Time to confirmed change**: The response threshold is exceeded in two or more consecutive assessments.
- **Time to sustained change**: The threshold for response is exceeded at one assessment and at all subsequent assessments until the end of the study / end of observation. If the follow-up time for the endpoint for which the responder analysis was performed is shortened, this change should be referred to as a "confirmed" change rather than a "sustained" change.

In case of relevant differences in observation time between treatment arms for an endpoint (e.g. due to early termination of observation due to disease progression), the time to first change should be reported in the German HTA dossier. Different observation periods between treatment arms are particularly relevant if they result in a different number of assessments for the respective endpoint. In such cases, the evaluation of time to confirmed or sustained change in the benefit assessment is usually not meaningfully interpretable.

If there are no relevant differences in observation time between treatment arms for an endpoint, the evaluation of the time to confirmed or sustained change is generally considered meaningful.

The method used to analyse the time to change should be contextually and conceptually justified by the pharmaceutical company.

5.6.2 Handling of deaths in analysis of deterioration in quality of life / symptoms

In longitudinal analyses of change magnitude, a MMRM is commonly used for cancer drug applications. However, further investigation and justification of underlying assumptions may be needed, particularly regarding the frequency and timing of death events.

Alternatively, cross-sectional analyses with a 'while alive' strategy are often applied, especially in palliative care. In these cases, regression models like ANCOVA at specific time points can compare treatment groups using the last measurement before death (Lawrance, et al., 2020).

Although a treatment-specific endpoint is required, responder analyses based on a Minimum Important Difference (MID) criterion for worsening quality of life or symptoms sometimes include death as a competing event in a composite endpoint (Charton, et al., 2019). However, such definitions are often deemed irrelevant to benefit assessment. In survival analysis, death should be treated as a competing event, as outlined in IQWiG's General Methods. The Cox model for cause-specific hazard functions is considered the correct approach, and Kaplan-Meier curves should be presented, with death treated as a censoring event. However, IQWiG's General Methods caution that the Kaplan-Meier curve may overestimate absolute risk in the context of competing risks, recommending the Aalen-Johansen estimator for cumulative incidence functions (CIF) instead (IQWiG, 2023). Both approaches are generally accepted in assessment practice.

The same considerations apply to analyses based on continuous changes from baseline in Patient-Reported Outcome (PRO) scores. Composite strategies, such as assigning the worst possible score at death, are typically not accepted in benefit assessments without adequate justification.

5.6.3 Clinical Relevance / Interpretability of MID

To assess the added benefit of a pharmaceutical intervention, the G-BA established a universal threshold of ≥ 15% of the scale range for all patient-reported outcomes (PROs). This threshold was initially recommended by IQWiG in 2021 and is grounded in a systematic review of the literature. The review revealed that benefit thresholds varied from 1% to 38% of the scale range across different disease areas. Based on these findings, and in pursuit of a standardized approach to PRO data evaluation, IQWiG determined that a ≥ 15% change in PRO scale range represents a "plausible threshold for a relatively small but sufficiently certain noticeable change." As such, further examination of the response criterion is not considered necessary when using this threshold.

However, exceptions exist for the EORTC questionnaires, where a 10-point response threshold is recommended. For the SF-36, a 10-point change aligns with the 15% criterion.

5.6.4 Hedges' g

An alternative to responder analysis with a MID threshold is the analysis of continuous data. In this case, relevance should be assessed using the standardized mean difference (SMD) in the form of Hedges' g, with an irrelevance threshold of 0.2. However, it is important to note that evaluating continuous data using mean differences and SMD for relevance does not replace the need for responder analysis. Both the G-BA and IQWiG emphasize the use of responder analyses with the specified threshold values.

5.6.5 Special considerations on indirect treatment comparisons

IQWiG generally recommends using adjusted indirect treatment comparisons (ITCs), particularly the Bucher approach, while unadjusted comparisons are typically rejected. The benefit assessment will be impacted when ITCs could not be conducted or may not be interpretable for patient-reported outcome measures (PROMs). Key challenges related to PROMs include, but are not limited to:

- **Data quality and consistency:** Variations in data collection methods, assessment tools, PRO assessment schedules, modes of assessment, confounding factors, and timing of data collection (pre- or post-intervention).
- **Handling of intercurrent events and missing data**: Lack of clear guidance on addressing these issues.
- **PROM endpoint selection and operationalization:** Challenges related to effect measures, divergent thresholds for responder definitions, and the choice of endpoints.

5.7 Current development and EU-HTA

Unlike preferred responder analyses with a predefined Minimal Important Difference (MID), the EU-HTAR Guidance on outcomes for joint clinical assessments recognizes plausible MIDs for endpoints derived from clinical research results. Anchor-based methods are considered the most suitable for estimating MIDs. The reporting requirements for Joint Clinical Assessment (JCA) include:

- **Responder definition**, if proposed, including estimation methods, perspective, and classification rules for patients.
- **References**, provided by the Health Technology Developer (HTD), to ensure full access to the bibliography justifying the responder definitions used.
- **Prespecified outcome measures**, defined as part of the primary analysis (e.g. on a continuous or categorical scale).
- Results expressed according to the responder definition, including summary and effect measures, as well as results based on the original quantitative scale.
- **Graphical representation of results**, such as cumulative distribution functions, which are strongly encouraged.

5.8 Recommendation

The IQWiG's general methods clearly outline the requirements for PRO in the German HTA process, which differ from those set for the EU-HTA Joint Clinical Assessment (JCA) process. However, the requirements set by IQWiG and G-BA for PRO in the German benefit assessment dossier should be appropriately implemented to demonstrate the drug's value.

To enhance the transferability of HTA assessments based on PRO measures for both national and European HTA processes and to minimize redundant efforts, it is crucial to harmonize these different approaches. This would also help reduce the volume of the “delta” dossier, which solely addresses national requirements.

6. Meta-analysis in German HTA

Authors: Sarah BÖHME, Annett KUCKA

6.1 Abstract

This section discusses the use of meta-analysis in the German benefit assessment process for evaluating the added benefit of new medical treatments. Meta-analysis, which synthesizes results from multiple studies, is crucial for drawing robust conclusions about the effectiveness of interventions. The process includes key methodological considerations such as defining the population, intervention, and relevant endpoints, and ensuring the quality of included studies. Meta-analyses must follow IQWiG's guidelines, utilizing random effects models and appropriate statistical methods like the Knapp-Hartung and Paule-Mandel approaches. The results are presented in a comprehensive manner, including forest plots and assessments of heterogeneity. The section highlights the importance of high-quality studies and addresses challenges in small study numbers, where Bayesian approaches may be employed starting in 2024. The use of meta-analysis provides statistical power, enhances precision, and facilitates the demonstration of added benefits in benefit assessments. Recommendations emphasize the need to adhere to IQWiG's methods, consider studies beyond regulatory approval, and prepare for the adoption of Bayesian meta-analysis in future assessments.

6.2 Introduction

Meta-analysis is a statistical method for summarizing the results of several studies within a systematic review. It typically uses publicly available aggregated study data (e.g., journals, HTA dossiers, assessment reports, and systematic literature reviews). An overall effect is calculated based on the effect sizes measured in individual studies, factoring in sample sizes and variances. More efficient methods are possible when individual patient data (IPD) are available, enabling evaluation at the patient level using fixed or random effects models, where studies are treated as effects rather than observational units.

In the German benefit assessment process, meta-analysis is considered when multiple studies are available to address a research question. The studies must be sufficiently comparable in terms of clinical (e.g., patient groups) and methodological (e.g., study design) factors. For a meta-analysis to be suitable for benefit assessment, the underlying data must be of high quality, with minimal bias and presented in a clear, transparent, and comprehensive manner, ensuring a well-supported conclusion.

6.3 Requirements of meta-analysis

The translation of all questions into a research question via a PICO helps to specify the data requirements and the framework for the assessment. The following points in particular must be considered:

- Definition of the population of interest (**P**),
- Definition of the intervention and comparator intervention of interest (**I** & **C**),
- Definition of all relevant endpoints (**O**),

- If applicable, the focused healthcare system or the geographical reference (e.g. Germany, Europe).

The underlying inclusion and exclusion criteria also play an important role in the benefit assessment. This should be considered when planning a meta-analysis.

All qualitatively sufficient and thematically relevant studies are considered. As a rule, at least 2 studies of high quality that were conducted independently of each other should be available.

The assessment of the general quality of studies is based on the AMSTAR (Shea, et al., 2009), the AMSTAR-2 (Shea, et al., 2017) or the ROBIS instrument (Siebert, 2005).

The results of a benefit assessment based on a meta-analysis are summarized in tabular form for each endpoint, if possible. If there are inconsistent results from several studies on an outcome, possible explanations for this heterogeneity are described (see Figure 4).

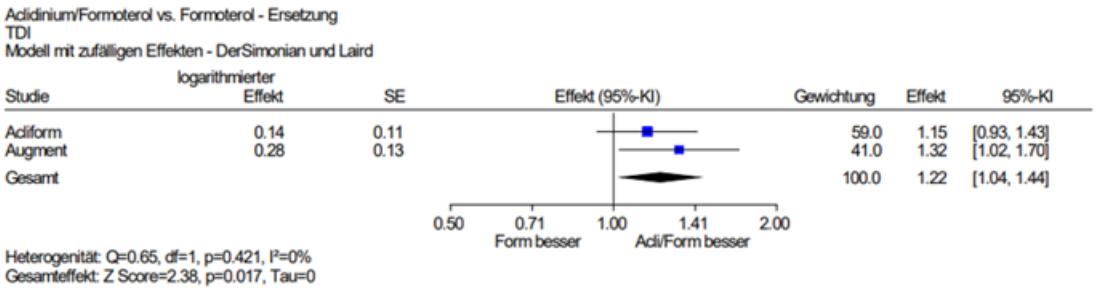


Figure 4: Meta-Analysis, COPD sympoms (TDI responder), aclidinium/formoterol vs. formoterol, effect measure: relative risk (IQWiG, 2015)

6.4 Methodology

According to IQWiG's General Methods, intention-to-treat (ITT) analysis results should be the primary basis for statistical evaluation. Meta-analyses should generally use random effects models, applying the Knapp-Hartung method, with the Paule-Mandel method for estimating heterogeneity. However, when only a small number of studies are available, heterogeneity may not be reliably estimated. If fewer than five studies are included, a fixed-effect model or a qualitative summary may be considered instead. In certain situations, alternative methods, such as Bayesian approaches or those from generalized linear models, may also be suitable. If the necessary estimates for location and dispersion are unavailable in the study documents, they should be independently calculated or approximated, as far as possible, based on the available information.

For continuous variables, the mean difference should be used as the effect measure, with Hedges' g for standardization where necessary. For binary variables, meta-analyses should primarily report both the odds ratio and the relative risk. In exceptional cases, other effect measures may be used. For categorical variables, the appropriate effect measure should be chosen based on the specific outcome and data available.

The effect estimates and confidence intervals should be displayed in forest plots. Heterogeneity of study results should be assessed using appropriate statistical measures, and these measures must always be specified, regardless of the heterogeneity outcome. If heterogeneity is not significant (e.g., p-value for heterogeneity statistic ≥ 0.05), the pooled effect with its confidence interval should be presented. In cases of significant heterogeneity, pooling of results should only occur in justified

exceptional cases. It is crucial to identify potential factors contributing to heterogeneity, which may include methodological and clinical factors, also known as effect modifiers (IQWiG, 2023).

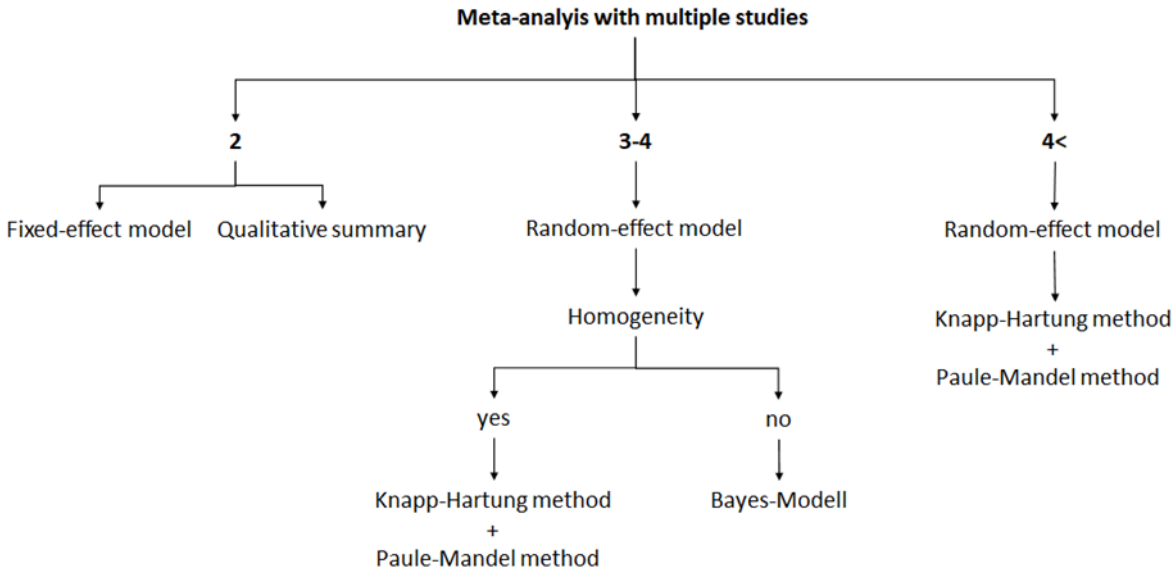


Figure 5: Methodology of the meta-analysis according to IQWiG General Methods 7.0

Table 1: Decision procedure for certainty of evidence in German benefit assessments (adopted from *(IQWiG, 2023)*)

		Number of studies				
		1 (with statistically significant effect)	**>=2**			
			Common effect estimate meaningful	Common effect estimates not meaningful		
			Meta-analysis statistically significant	Clear	Moderate	No
Qualitative certainty of results	High	Indication	Proof	Proof	Idication	-
	Moderate	Hint	Indication	Indication	Hint	-
	Low	-	Hint	Hint	-	-

6.5 Current status in the German benefit assessment

Meta-analyses typically offer greater statistical power due to the inclusion of multiple studies, resulting in a larger overall sample size. This increased power enhances the reliability and precision of the effect estimates, making it easier to detect significant treatment effects that may not be evident

in individual studies. When conducted following the prescribed methodological standards, meta-analyses can provide robust evidence of the effectiveness of a new drug.

If the meta-analysis demonstrates significant benefits of the drug over existing treatments or placebo, it can lead to a quantifiable added benefit, which plays a crucial role in the German benefit assessment process. A clear, evidence-based assessment of this added benefit is essential for informing healthcare policy decisions, reimbursement strategies, and drug pricing. Furthermore, meta-analyses can consolidate results from diverse populations, study designs, and clinical settings, offering a more comprehensive view of the drug's effectiveness across different groups.

However, to ensure that these findings are meaningful and lead to a legitimate added benefit, it is vital that the underlying studies are of high quality, and that the meta-analysis is performed rigorously, addressing issues like heterogeneity and potential biases. By adhering to the IQWiG guidelines and conducting thorough sensitivity analyses, manufacturers can strengthen their evidence base, increasing the likelihood of demonstrating significant added benefit in the benefit assessment process.

6.6 Current development

A meta-analysis can be employed to synthesize and integrate the findings of multiple studies on a specific research question. In the majority of benefit assessments, dossiers comprising a meta-analysis are submitted with a limited number of studies. In such instances, the standard methods for meta-analyses, random-effects models, exhibit unfavourable characteristics when only a small number of studies (2-4) are available. Consequently, methodological approaches are being examined with a view to enabling more reliable assessment of the benefits of medical treatment measures than was previously possible when fewer studies were available.

Due to the limited number of studies, the assessment of the benefit is accompanied by uncertainty due to the heterogeneity between the studies. Given the uncertainty, the extent of the added benefit could often not be quantified. A novel approach is now to be employed. Considering recent developments, IQWiG, in collaboration with the University of Göttingen, has identified a potential avenue for utilising information from previous benefit assessments. A model for deriving the requisite preliminary information (so-called a priori distributions) was published at the beginning of 2023. The recently published article in the journal Research Synthesis Methods builds upon this foundation (Lilienthal, et al., 2024).

Although it is not yet included in the current version of their general methods, IQWiG will be using the Bayesian meta-analysis approach to assess benefits from November 2024 onwards. Manufacturers can seek guidance from (G-BA FAQ, 2024), where the following standard procedure to carry out meta-analyses is recommended, unless there are clear reasons against it:

- 2 studies: Application of the fixed-effect model, using the inverse variance method for continuous data or the Mantel-Haenszel method for binary (IQWiG, 2023).
- 3-4 Studies: Application of the random-effects model using a Bayesian meta-analysis with non-informative a priori distributions for the treatment effect and informative a priori distributions for the heterogeneity parameter according to (Lilienthal, et al., 2024). In addition, a comparison with a qualitative summary of the study results should be carried out using the concept of implied effects (IQWiG, 2023).
- 5 Studies and more: Application of the model with random effects using the Knapp-Hartung method and the Paule-Mandel method for heterogeneity estimation (Veroniki , et al., 2015)

It can be assumed that IQWiG will include this new approach as standard in its catalogue of methods with the next revision of the general methods.

6.7 Recommendation

In the context of the German benefit assessment and according to the principles of evidence-based medicine, relevant evidence (i.e., clinical studies) must be identified through systematic literature searches. The identified pool of studies may extend beyond those directly related to regulatory approval in the EU. For example, studies conducted solely in the Asian region may also be relevant for the benefit assessment and must be evaluated for their relevance and suitability for meta-analysis.

If multiple studies are available to address the research question, the manufacturer is required to consider conducting a meta-analysis. IQWiG's methodological requirements are clearly outlined and must be followed to ensure the acceptance of the meta-analysis.

In 2024, a new methodological approach for meta-analyses with few studies was introduced, utilizing a Bayesian approach and empirically derived priors. It is expected that this method will become the standard for meta-analyses involving 3 or 4 studies in future benefit assessments. Therefore, manufacturers and CROs should begin preparing for the planning and application of this methodology.

7. Quantification of an added benefit without Head-to-Head Data – Historical comparisions

Authors: Astrid GENET, Annett KUCKA

7.1 Abstract

This section discusses the use of historical comparisons in the German benefit assessment process when only single-arm trials are available for a new drug. Historical comparisons are essential for meeting the G-BA's requirements when randomized controlled trials (RCTs) are not possible. Key acceptance criteria include study similarity, confounder adjustment, larger sample sizes, dramatic effect sizes, and the use of serious endpoints. The most suitable use cases for historical comparisons are diseases with severe outcomes, where substantial differences in treatment effects can be observed. The section highlights the specific role of historical comparisons in orphan drug status cases, where even without clear evidence, a non-quantifiable added benefit is regularly granted. Despite the challenges and strict evaluation by IQWiG and the G-BA, historical comparisons can still provide valuable evidence in the absence of RCTs, particularly for rare diseases and innovative therapies, potentially enhancing the treatment's value proposition. Recommendations emphasize that while proving an added benefit may be difficult, historical comparisons remain a crucial tool for benefit assessments.

7.2 Introduction

When only single-arm trials are available for the benefit assessment of a new drug, historical comparisons are the only means to compare the new compound to the comparator and meet the G-BA's requirements.

7.3 Acceptance criteria

To claim an added benefit based on a historical comparison, the IQWiG prerequisites are clear:

- **Study Similarity:** As with any indirect comparison, the studies must be highly comparable in terms of design and populations.
- **Confounder Adjustment:** In the absence of randomization, differences in potential confounders (factors influencing both treatment and endpoints that could distort treatment effects) cannot be excluded and must be adjusted for when estimating effects.
- **Larger Sample Sizes:** Confounder adjustment typically requires larger sample sizes than randomized trials.
- **Effect Size Requirement:** Due to the possibility of unknown confounders, a dramatic effect is essential to establish a benefit. Specifically, the difference between arms must be at least a factor of 5 to 10 (RR >5-10; HR < 0.2-0.1).
- **Serious Endpoints:** Even with a dramatic effect, evidence from historical comparisons can only be considered for serious endpoints (e.g., mortality, severe symptoms or complications, adverse events, and health-related quality of life). For lower endpoints, even more substantial differences would be needed to demonstrate clinically meaningful effects.

The requirement for a dramatic effect makes historical comparisons mostly suitable for diseases with very serious outcomes (e.g., high mortality rates), where no or highly ineffective therapy options exist. In such cases, the comparator is typically "best supportive care." For example, a relative risk (RR) of 5-10 for a mortality endpoint with 0% survival in the comparator arm would necessitate at least 80-90% survival in the active arm. In contrast, a 50% survival rate in the comparator arm would require at least 90-95% survival in the treatment arm. These drastic survival differences are typically seen in rare diseases, where innovative therapies may qualify for orphan drug status.

7.4 Historical comparisons in the benefit assessment procedure

As of April 2024, historical comparisons were part of 47 AMNOG submissions, of which 17 (36%) involved therapies with orphan drug status. Of these 47 submissions, only a minority (12, 25.5%) resulted in an added benefit.

Regarding the extent of the added benefit, the majority (7, 58%) were classified as non-quantifiable, while 3 (25%) were deemed major, 1 considerable, and 1 minor. In all cases, the G-BA acknowledged very large effects (referred to as "dramatic" or "very large" in the G-BA resolution) in one or more serious endpoints, considering these effects large enough to rule out chance as the sole explanation. The indications primarily involved metabolic diseases (50%), with the remainder distributed among oncological, infectious, hematopoietic, and nervous system disorders.

Most submissions (74.5%) did not result in an added benefit based on historical comparisons. However, 37% of those submissions received a non-quantifiable added benefit, not due to the data but because of their orphan drug status. This reflects the special status of orphan drugs in the German benefit assessment process: to encourage the development and commercialization of such therapies, the added benefit for orphan drugs is established upon marketing authorization. While the G-BA determines the extent of the added benefit, orphan drugs are guaranteed at least a non-quantifiable added benefit upon market entry, regardless of the evidence provided in the dossier.

7.5 Recommendation

The practical requirements for historical comparisons face significant challenges and are strictly evaluated by IQWiG and the G-BA. However, in the absence of randomized controlled trials (RCTs), particularly for orphan drugs and ATMPs, historical comparisons may be the only viable method to present a comparison with the appropriate comparator therapy.

Given this context, although the likelihood of proving an added benefit is low and depends on demonstrating very strong effects for major endpoints, conducting and presenting a historical comparison can still be a valuable option when it represents the best available evidence. Even without a dramatic effect or the potential for a quantifiable benefit, such a comparison can highlight the potential of the new treatment and strengthen the value proposition within the dossier.

8. Definition and validation of Surrogate Endpoints

Authors: Robert BAUER, Sarah BÖHME

8.1 Abstract

This chapter discusses the validation of surrogate endpoints within the benefit assessment process in Germany. It provides an overview of accepted surrogate endpoints and highlights the challenges in fulfilling the requirements for the formal validation of additional surrogate endpoints. Methodological and practical considerations for surrogate endpoint validation are provided, including examples from previous benefit assessments. An outlook to EU-HTA is provided as well as recommendations and conclusions. Importantly, it is recommended to consider the acceptance of endpoints for HTA already at study planning stage (e.g., by taking advantage of early consultations including G-BA advice). Due to the strict requirements for surrogate endpoint validation, it is advisable to rely on already accepted endpoints whenever possible.

8.2 Introduction

Within the benefit assessment processes in Germany there is a clear distinction in terms of acceptance of the different endpoint types used in clinical studies. Whereas endpoints defined as patient-relevant (refers to how a patient feels, functions or survives) (IQWiG, 2021) are accepted, a surrogate endpoint can as per of Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) General Methods be regarded as valid only if the effect of an intervention on the patient-relevant outcome to be substituted is explained to a sufficient degree by the effect on the surrogate endpoint.

As a consequence, many endpoints that are important for regulatory submissions and regarded as patient-relevant by other HTA agencies are not necessarily relevant for the German benefit assessment. Such endpoints do require a formal surrogate endpoint validation which has to fulfill the specific requirements described in IQWiG General Methods (IQWiG, 2023). Examples of endpoints that are currently not seen as valid surrogates for any intervention include as well intermediate outcomes as e.g. progression-free survival (PFS) in oncology, imaging results and related outcomes (response) and biomarkers as e.g. HbA1c for interventions in type 2 diabetes mellitus.

Altogether, there are at the moment only a few examples of surrogate endpoints that have been accepted as valid within the benefit assessment (see Table 2). However, all previous formal attempts by a pharmaceutical company to provide sufficient evidence to validate and apply additional surrogate endpoints have failed. This was either due to methodological concerns raised by IQWiG or the association between surrogate and patient-relevant endpoint was deemed to be not strong enough.

Methodological and practical considerations around surrogate endpoint validations are provided along with examples from previous benefit assessments in Germany. In addition, a high-level comparison of EU-HTA guidance around surrogate endpoints and IQWiG General Methods is provided.

Table 2: Overview of surrogate endpoints and the related benefit assessment procedures in which the surrogate endpoints had initially been accepted in the benefit assessment (Ring, et al., 2019)

Indication	Surrogate endpoint	Patient-relevant endpoint	Related benefit assessment
HIV infection	Virological response	Composite of "AIDS defining disease" and death	Rilpivirin (IQWiG, 2012)
	CD4 cell count	Composite of "AIDS defining disease" and death	Elvitegravir/Cobicistat/ Emtricitabin/ Tenofovirdisoproxil (IQWiG, 2013)
Systemic lupus erythematosus	Reduction of oral glucocorticoids	Avoidance of side effects related to glucocorticoids use	Belimumab (G-BA, 2012)
Asthma	Reduction of oral glucocorticoids	Avoidance of side effects related to glucocorticoids use	Mepolizumab (IQWiG, 2016)
Type 1 diabetes mellitus	Change in HbA1c	Microvascular complications	Insulin degludec (IQWiG, 2015)
Hepatitis C	Sustained Virological Response	Hepatocellular carcinoma	Sofosbuvir/Velpatasvir (IQWiG, 2016)

8.3 G-BA and IQWiG approach to surrogate endpoint validation

The German HTA guidelines allow the usage of surrogate endpoints within the benefit assessment and specify detailed requirements for applicants in (G-BA, 2021) and (IQWiG, 2023). IQWiG states that surrogate endpoints are frequently used in medical research and claims that most surrogate endpoints are unreliable as a substitute for patient-relevant outcomes. IQWiG further states, that these endpoints can normally only be considered in the benefit assessment if they are validated beforehand by means of appropriate statistical methods. In that regard methods described in (Burzykowski, et al., 2005) (Burzykowski & Buyse, 2006) and (Molenberghs, et al., 2009) are mentioned both in (IQWiG, 2023) and (IQWiG, 2021). These correlation-based meta-analytic methods are applicable both on individual patient data (IPD) level and on aggregated data level. The surrogate threshold effect (STE) is preferred as a concept applicable in less conclusive situations.

Both (G-BA, 2021) and (IQWiG, 2023) further state that studies included in the surrogate endpoint evaluation should be conducted within a sufficiently restricted patient population and within comparable interventions (e.g. drugs with a comparable mode of action).

For the final assessment of surrogate endpoints IQWiG specifies detailed decision criteria including a boundary of 0.85 for the validation of surrogate endpoints based on a correlation coefficient (IQWiG, 2023). As typical for other situations (e.g. Hedge's g) in (IQWiG, 2023) this boundary is not applied to the estimate itself but to the lower level of its interval estimate (in this case the 95% prediction interval). This practice of applying the correlation threshold of 0.85 to the lower limit of the 95% prediction interval instead of the point estimate lowers the probability of successfully validating a surrogate endpoint.

8.4 Practical considerations around surrogate endpoint validations

The focus of this section will be on practical considerations around surrogate endpoint evaluations. Methodological aspects are described elsewhere, for example in the references mentioned in the previous section.

As stated in the previous section surrogate endpoint evaluations should be conducted within a sufficiently restricted patient population and within comparable interventions. However, in practice, most of the time it is unlikely to both fulfill these requirements and at the same time identify a sufficient number of studies for the required correlation-based meta-analysis. The literature discusses using smaller units within a study for the meta-analysis instead of the study level. Examples of these units include regions. However, studies are typically not powered for the corresponding treatment comparisons on unit level (Buyse et al., 2016; Geybels et al., 2021).

Altogether, only in situations where a therapy of the same class and in the same indication has been on the market for already a longer time, a sufficient study pool might be available for surrogate endpoint evaluation. An example is the case of the antibody drug conjugate trastuzumab emtansine where study data from previous trastuzumab studies could be incorporated in the surrogate endpoint validation study (IQWiG, 2020).

Furthermore, sensitivity analyses are important to assess the robustness of the surrogate endpoint evaluation. For example, inclusion or exclusion of studies from the study pool with potential differences in terms of population, design or interventions can be considered.

Optimizing Surrogate Endpoint Validation with IPD

According to the IQWiG General Methods for correlation-based procedures, two key conditions are required to demonstrate the validity of a surrogate endpoint:

1. **High correlation between the surrogate endpoint and the patient-relevant outcome at the individual patient data (IPD) level.**
2. **High correlation between effects on the surrogate and effects on the patient-relevant outcome at the study level.**

Incorporating IPD significantly increases the complexity of surrogate endpoint validation, especially when including studies from other sponsors (e.g., investigator-initiated studies). Several key points must be considered:

1. Identification of Relevant Studies

A systematic literature review is essential to identify studies for surrogate endpoint validation.

2. Access to IPD from Other Sponsors

Once relevant studies are identified, a detailed plan is required to obtain IPD from other sponsors. Collaborations with independent research groups or trusted third parties are crucial.

3. Defining Necessary Variables

Clearly defining the required variables is important. The smaller the variable set, the less cleaning effort is needed, and the greater the likelihood of data sharing.

4. Data Management Efforts

Data management tasks, such as establishing data standards and programming, can be time-consuming. Additionally, queries arising during data review can further delay progress.

8.5 Surrogate validation via meta-regression based on aggregated study data

Access to IPD for all relevant studies identified in the systematic literature review as described above is not always feasible. In these situations, a meta-regression based on aggregated data can be conducted as an alternative. According to Schürmann and Sieben a meta-regression model based on aggregated data reveals a conservative estimation of the STE compared to IPD-based meta-regression models (Schürmann & Sieben, 2015).

In general, the requirements for surrogate endpoint validations are the same for validations based on IPD and validations based on aggregated data. However, besides a more conservative estimation of the STE, the level of information available for each study is lower and consideration of additional variables beyond the published data is not possible. Given the conservative estimation of the STE it has been shown that an unrealistic high number of studies is needed to overcome the threshold of high correlation (Gillhaus, et al., 2017).

In situations where IPD are available from some but not all studies in the study pool, the correlation between the surrogate and the patient-relevant outcome at the individual patient-data level might be shown for the available IPD studies and the correlation between effects on the surrogate and effects on the patient-relevant outcome at a study level might be shown based on all aggregated data in a meta-regression.

8.6 Experience from previous German HTA procedures

As previously mentioned, all formal attempts by pharmaceutical companies to provide sufficient evidence for validating and applying surrogate endpoints have failed. These failures were mainly due to methodological concerns raised by IQWiG, such as issues with the study pool used in meta-analyses, or because the correlation between the surrogate and patient-relevant endpoints was deemed insufficient (either at the correlation or STE level).

Examples include:

- The assessment of Pertuzumab and Trastuzumab Emtansine in adjuvant breast cancer, where disease-free survival was evaluated as a surrogate for overall survival (IQWiG, 2018), (IQWiG, 2020).
- The assessment of Palbociclib in metastatic breast cancer, where progression-free survival was evaluated as a surrogate for overall survival (IQWiG, 2017), (IQWiG, 2017).

8.7 Current development and EU-HTA

Although the decision on the acceptance of surrogate endpoints for the appraisal remains with the Member States on the national level, the EU-HTA guidance on outcomes for joint clinical assessment (JCA) (HTA CG, 2024) includes considerations on surrogate outcomes and specifies three levels of evidence for surrogacy

- Level 1: evidence demonstrating that treatment effects on the surrogate outcome correspond to effects on the patient-centered outcome

- Level 2: evidence demonstrating a consistent association between the surrogate outcome and the final patient-centered outcome
- Level 3: only evidence of the biological plausibility of an association between the surrogate outcome and the final patient-centered outcome).

Level 1 and 2 are currently required for surrogate endpoint evaluation within the benefit assessment in Germany. In addition, it might also be assumed that the methodological requirements described in IQWiG General Methods will stay relevant in future for HTA in Germany.

Regarding the requirements for the correlation coefficient the guidance states that a correlation of at least 0.85 is described as “high” and can be used as a criterion for validation of surrogate outcomes (HTA CG, 2024). However, assessors in Germany might potentially still apply this threshold to the lower level of the 95% prediction interval. As in IQWiG general methods, considerations on the surrogate threshold effect are also included in the EU-HTA guidance.

An investigation was conducted by (Ciani, et al., 2021) into the validity of surrogate endpoints across eight international HTA agencies (including Germany), which revealed that IQWiG appears to adopt a notably stringent stance with regard to the acceptability of surrogate endpoints. As previously mentioned, it can be hypothesised that this approach will also be implemented in future HTA processes in Germany.

8.8 Recommendation

When planning for a clinical study program, it is important to consider the acceptability of the study endpoints by HTA agencies and take advantage of the opportunity for early consultations (e.g. G-BA advice). Due to the strict requirements for surrogate endpoint evaluation, it is advisable to rely on endpoints already considered as patient-relevant by G-BA whenever possible.

If there is still a need to include surrogate endpoints in the HTA dossier, the corresponding surrogate endpoint validation requires thorough planning. Conduct of a feasibility study, in which the available study pool is determined, is recommended. In addition, the feasibility study should assess the probability of success for the surrogate endpoint evaluation based on the IQWiG criteria for the correlation coefficients.

The statistical methodology preferred by IQWiG requires the use of IPD. Especially, when studies from other sponsors are to be included (e.g., investigator-initiated studies) the related efforts to incorporate the data increase substantially. The use of aggregated data e.g., in a meta-regression model is in general possible but has substantial limitations. In any case, the conduct of sensitivity analyses is advisable, e.g. by applying different inclusion and exclusion criteria for the study pool.

9. Routine Practice Data Collection for the use of new pharmaceuticals

Authors: Susanne HUSCHENS, Annett KUCKA

9.1 Abstract

Some medicinal products, including those with conditional marketing authorizations, those authorized under exceptional circumstances, and orphan drugs, receive limited clinical trial data upon marketing authorization but still obtain approval from the CHMP and the European Commission (EC). Despite insufficient data for benefit assessment in Germany, these products undergo a benefit assessment by the G-BA. In such cases, the G-BA may require the collection of real-world data to compare the product with its defined treatment comparators. This data helps enhance the evidence for benefit assessment, including its performance in daily practice.

Routine Practice Data Collection (AbD), initiated in 2020, involves gathering data through disease registries or newly established data collection methods. The information collected is crucial for assessing the benefits and potential risks of products, which directly impacts reimbursement negotiations with the National Association of Statutory Health Insurance Funds (GKV-SV). Products with limited clinical trial data, especially those for rare or life-threatening conditions, may require AbD to confirm their benefit-risk profile.

AbD procedures are regulated under Section 35a of SGB V and are initiated for specific products, such as those covered under Regulation (EC) No 726/2004 and Regulation (EC) No 141/2000. While AbD procedures can begin before approval, they are typically implemented post-market authorization and benefit assessment. Current experience indicates that some AbD procedures are triggered by urgent regulatory needs, while others are initiated post-assessment in response to new information or changes in conditions.

As the process continues to develop, timelines for the concept development, participation procedures, and data collection have been established, although precise timeframes are still evolving. Despite the complexity and the lengthy nature of AbD procedures, they play a vital role in ensuring that medicines with limited clinical trial data undergo thorough real-world evaluations. Initially launched in 2020 for individual cases, the number of AbD evaluations is steadily increasing, with the process continuing to adapt as more experience is gained.

9.2 Introduction

Some medicinal products receive limited data upon marketing authorization application but still obtain a positive opinion from the CHMP and approval by the European Commission (EC). These include:

- Medicinal products with conditional marketing authorization
- Medicinal products with authorization under exceptional circumstances
- Orphan drugs for rare diseases

Although clinical trial data for these products may be insufficient for benefit assessment and deriving an added benefit in Germany, they still undergo a benefit assessment by the G-BA. In such cases, the G-BA may require the pharmaceutical company to collect real-world data comparing the product to its defined treatment comparators. This process, known as AbD, aims to enhance the evidence

supporting the benefit assessment by gathering data on the product's performance in daily practice, including comparisons with other treatments.

9.3 What is Routine Practice Data Collection (AbD)?

Starting in 2020, the G-BA may require pharmaceuticals with limited data to document their use and collect data. Typically, this data is gathered through an existing or newly established disease registry. Routine data provides valuable insights into the benefits and potential harms of the product. The findings from this assessment are crucial for subsequent price negotiations with the National Association of Statutory Health Insurance Funds (GKV-SV).

9.4 Why is it sometimes necessary to collect data during use?

All pharmaceuticals available in German pharmacies or hospitals have an official marketing authorization, which undergoes stringent control. Clinical data is used to ensure that the benefits of a product outweigh its risks, confirming its effectiveness and adherence to pharmaceutical quality standards. Only when these criteria are met is the product authorized for sale.

However, for certain medicines, especially those used to treat rare or life-threatening conditions, only limited data may be available at the time of approval due to the lack of alternatives. In such cases, the G-BA may require an AbD to gather further evidence of the product's benefits and risks.

AbD procedures are regulated under Section 35a paragraph 3b of SGB V. The G-BA may require a pharmaceutical company to submit data collection and analysis for benefit assessment within a predefined period for the following products:

- Products subject to the procedure in Article 14(8) of Regulation (EC) No 726/2004 (as amended by Regulation (EU) 2019/5)
- Products authorized for the treatment of orphan conditions under Regulation (EC) No 141/2000

While AbD procedures can be initiated before approval, most are implemented after the product is already on the market and has undergone initial benefit assessment. For further details, refer to Table 3.

Table 3: Procedure of Routine Practice Data Collection according to Section 35a paragraph 3b SGB V as of 18.12.2024

Medicinal substance	Indication	Pharmaceutical company	Start of procedure of Routine data collection	Planned re-evaluation of the benefit assessment	Link to the procedure of Routine data collection	Link to the procedure of benefit assessment
Procedure initiated						
Exagamglogen Autotemcel	Sickle-cell disease	CRISPR Therapeutics; Vertex Pharmaceuticals GmbH	01.06.2023	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/9/	No benefit assessment so far
Epcoritamab	Relapsed or refractory follicular lymphoma	AbbVie Deutschland GmbH	04.04.2024	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/15/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1004/
Fidanacogen elaparvovec	Haemophilia B	Pfizer Pharma GmbH	05.10.2023	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/11/	No benefit assessment so far
Iptacopan	Paroxysmal Haemoglobinuria	Novartis Pharma GmbH	01.08.2024	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/17/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1095/
Odronextamab	Relapsed or refractory follicular lymphoma	Regeneron GmbH	01.02.2024	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/13/	No benefit assessment so far

Medicinal substance	Indication	Pharmaceutical company	Start of procedure of Routine data collection	Planned re-evaluation of the benefit assessment	Link to the procedure of Routine data collection	Link to the procedure of benefit assessment
Odronextamab	Relapsed or refractory diffuse large B-cell lymphoma	Regeneron GmbH	01.02.2024	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/14/	No benefit assessment so far
Data collection required						
Talquetamab	Relapsed and refractory multiple myeloma, at least 3 previous therapies	Janssen-Cilag GmbH	19.10.2023	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/12/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/997/
Ongoing data collection (date of start of routine data collection)						
Brexucabtagen-Autoleucel (21.08.2023)	Relapsed or refractory mantle cell lymphoma	Gilead Sciences GmbH	07.10.2021	21.07.2028	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/5/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/657/
Etranacogen Dezaparvovec (30.08.2024)	Haemophilia B	CSL Behring GmbH	04.08.2022	02.11.2029	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/4/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/953/
Onasemnogen-Abeparvovec (01.02.2022)	Spinal muscular atrophy	Novartis Gene Therapies EU Limited	16.07.2020	01.07.2027	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/1/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/689/
Risdiplam (30.10.2024)	Spinal muscular atrophy	Roche Pharma AG	07.10.2021	01.04.2028	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/3/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/680/

Medicinal substance	Indication	Pharmaceutical company	Start of procedure of Routine data collection	Planned re-evaluation of the benefit assessment	Link to the procedure of Routine data collection	Link to the procedure of benefit assessment
Valoctocogen Roxaparvovec (30.08.2024)	Haemophilia A	BioMarin International Ltd.	03.02.2022	02.11.2029	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/2/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/877/
Procedure overridden						
Fedratinib	Myelofibrosis	Bristol Myers Squibb GmbH	21.10.2021	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/6/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/662/
Procedure terminated by G-BA						
Brexucabtagen-Autoleucel	B-cell precursor acute lymphoblastic leukaemia	Gilead Sciences GmbH	03.11.2022	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/7/	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/878/
Exagamglogen Autotemcel	Beta-thalassaemia	Vertex Pharmaceuticals GmbH	06.07.2023	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/10/	No benefit assessment so far
Marstacimab	Haemophilia A and B	Pfizer Pharma GmbH	04.04.2022	-	https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/16/	No benefit assessment so far
Abbreviation: G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss); SGB V: Social Code Book 5						

9.5 How does the procedure work?

The process begins with the G-BA, the highest body of self-administration in the German healthcare system, determining whether a Routine Practice Data Collection (AbD) is necessary for the drug. If the G-BA initiates an AbD procedure, the Institute for Quality and Efficiency in Healthcare (IQWiG) is tasked with developing a detailed concept within 3 to 5 months. This concept includes key elements such as the Population, Intervention, Comparison, Outcome (PICO), data collection duration, scope, and the methodology for data analysis.

Following the concept development, the G-BA finalizes the details and formally requests the accompanying data collection. Subsequently, the drug manufacturer creates a study concept, which is then reviewed by the G-BA at least every 18 months. If sufficient data becomes available, the G-BA reviews it, and the drug undergoes a new benefit assessment.

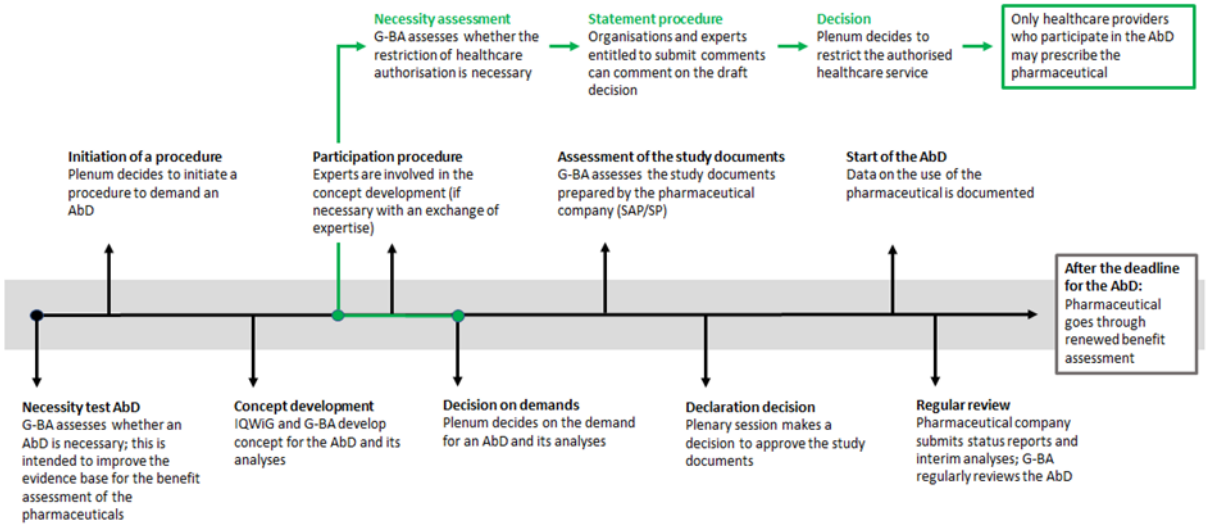


Figure 6: Process of AbD by the G-BA

Current experience with the AbD process is still being gathered, and as such, the development of a structured procedure and precise timelines is ongoing. Consequently, it is difficult to provide exact timeframes at this stage. Some AbD procedures are initiated prior to authorization and benefit assessment due to urgent regulatory needs or to meet deadlines and minimize risks. Conversely, other AbD procedures are initiated during or after the benefit assessment, typically triggered by new information or changing conditions that arise post-assessment.

The following approximate timelines are based on current practices:

- Concept development: Should be completed within 6 months.
- Participation procedure (written statement): Must be submitted within 4 weeks of receiving the request.

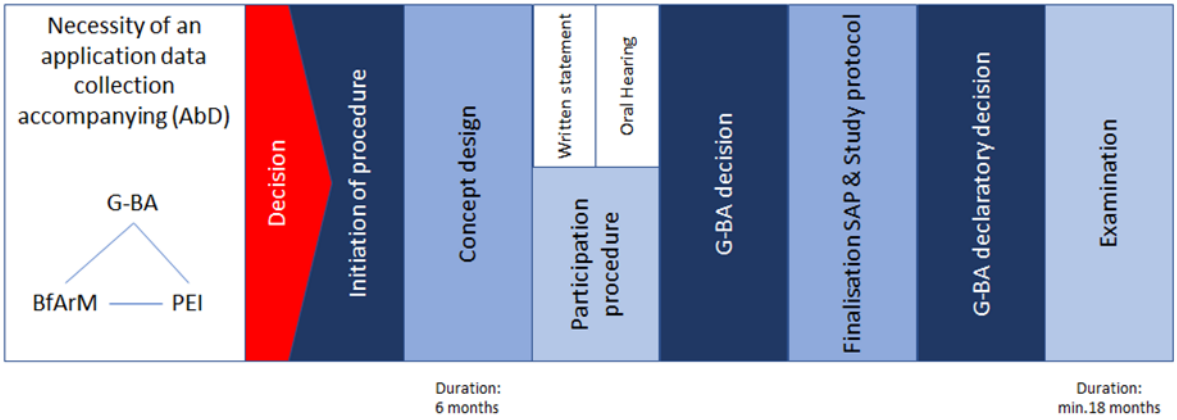


Figure 7: Procedure for AbD in Germany

Steps in the Application Data Collection (AbD) Procedure by the G-BA:

1. G-BA Decision: The process starts with the G-BA determining whether an application data collection is needed.
2. Initiation of Procedure: The procedure is officially initiated if the G-BA decides that an AbD is necessary. This step includes consultations with relevant authorities, such as the BfArM (Federal Institute for Drugs and Medical Devices) and the PEI (Paul Ehrlich Institute) in the case of biologicals.
3. Concept Design: The concept design phase outlines the study and data collection plan.
4. Study Protocol & G-BA Approval: The study protocol is finalized and must be approved by the G-BA. A declaratory decision might be issued.
5. Examination: Following the G-BA decision and approval, an examination of the data and studies is carried out, potentially over a period of 18 months.

9.6 Current development

Determining whether a medicinal product is eligible for an AbD depends on various factors, which can vary from case to case. For instance, the G-BA may require an AbD based on orphan drug status or other criteria. Additionally, a prior benefit assessment is not always necessary. While in the early years, starting from 2020, only individual procedures were initiated, an increasing number of AbD evaluations are now being conducted.

9.7 Conclusion

The methodological requirements for an AbD are stringent and challenging to implement. In some cases, the level of rigor required for an AbD may involve planning a controlled study similar to clinical trials, which goes beyond the usual practices for healthcare studies. Moreover, these studies are often so complex that it can take years before they are even initiated. Comparative disease registries are often desired, but the concept of such registries may conflict with the specific requirements set by the authorities, including the need for precise endpoints and data collection methods. Additionally, since the process is still in development, no results are currently available from these efforts. Despite these challenges, the AbD process is critical for gathering real-world evidence for medicinal products with limited clinical trial data, especially in cases involving orphan drugs or

conditional marketing authorizations. Initially, from 2020 onwards, individual AbD procedures were initiated, but now an increasing number of evaluations are being conducted as the process continues to evolve.

10. Cost-benefit assessment of drugs according to Section 35b SGB V

Author: Annett KUCKA

10.1 Abstract

This section outlines the purpose and process of cost-benefit assessment (Kosten-Nutzen-Bewertung, KNB) in Germany as defined in § 35b of the German Social Code, Book V (SGB V). The KNB is intended to provide an economic perspective to support AMNOG procedures, particularly during reimbursement negotiations.

A KNB can be requested either by the National Association of Statutory Health Insurance Funds (GKV-SV) or by the pharmaceutical company (pU), even in cases where the Federal Joint Committee (G-BA) has not determined an added benefit. However, since the introduction of the AMNOG process in 2011, neither the statutory health insurers nor the pharmaceutical industry have initiated a KNB. Consequently, the Institute for Quality and Efficiency in Health Care (IQWiG) has not yet been commissioned by the G-BA to conduct such an assessment under § 35b SGB V.

Typically, a KNB includes the calculation of the incremental cost-effectiveness ratio (ICER) and a budget impact analysis. It does not provide an explicit price recommendation for medicinal products. Instead, it enhances transparency regarding cost-efficiency and offers a technical foundation for reimbursement decisions.

As the body commissioned by the G-BA, IQWiG is responsible for conducting the KNB according to international standards of evidence-based medicine and health economics. Recent methodological updates suggest that Germany is increasingly aligning itself with international norms in cost-effectiveness assessment. Since evolving methodology may pave the way for its future implementation, continued monitoring is recommended.

10.2 Introduction

The objective of the KNB is to provide a concise overview of economic data to support the AMNOG procedure, particularly during reimbursement negotiations. Section 35b SGB V allows for a KNB to be conducted in three specific situations:

1. The National Association of Statutory Health Insurance Funds (GKV-SV) or the pharmaceutical company (pU) can request a KNB through the arbitration board.
2. The pharmaceutical company (pU) may submit a KNB application when the G-BA does not identify an added benefit for the new drug, and the company assumes responsibility for the financial cost of the KNB.
3. The IQWiG (Institute for Quality and Efficiency in Health Care) can conduct the KNB as part of its broader mandate to analyze the quality and efficiency of healthcare services under the GKV-SV framework.

The KNB analysis typically includes calculating the Incremental Cost-Effectiveness Ratio (ICER), which compares the additional costs of a new treatment to the benefits it provides in terms of health outcomes. Along with ICER, a budget impact analysis is often included to assess the financial implications of introducing the new drug into the healthcare system. However, the primary goal of

the KNB is not to recommend a specific price for the drug but to increase transparency about its cost-effectiveness relative to other treatments in the same indication area.

The G-BA can task the IQWiG with conducting the cost-benefit assessment, as illustrated in Figure 10 (IQWiG, 2023), according to Section 35b SGB V.

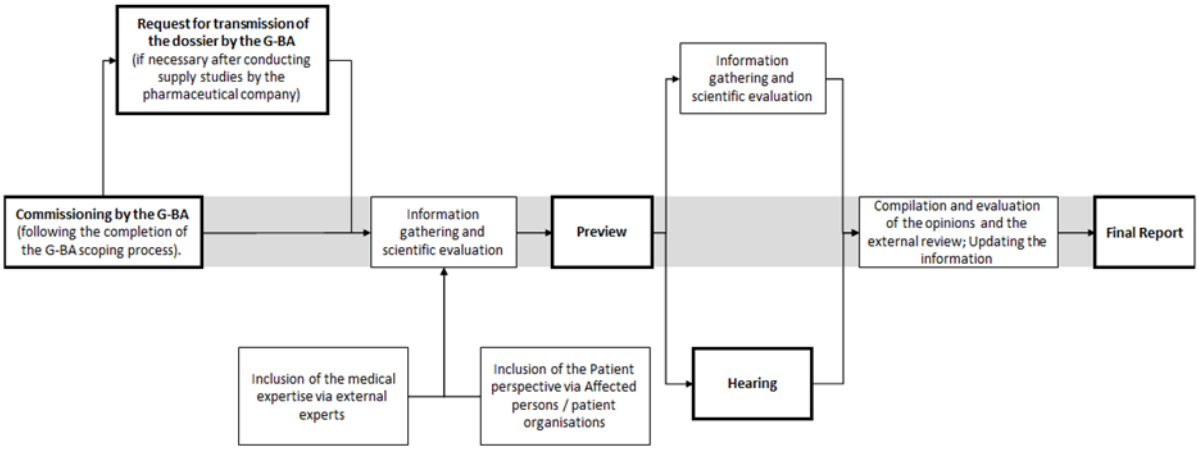


Figure 8: Procedure for preparing a cost-benefit assessment in accordance with Section 35b SGB V

The process for preparing a KNB involves IQWiG defining the appropriate methods and criteria, ensuring alignment with international standards of evidence-based medicine and health economics. The findings from the KNB can complement the benefit assessment by offering a broader economic evaluation that integrates key health economic data, contributing to the reimbursement decision process.

10.3 Current Development

Recent developments suggest that Germany is moving towards a more regular and systematic approach to assessing the cost-benefit of new technologies and pharmaceuticals, with IQWiG updating its methodology for cost-benefit assessments as part of the General Methods 7.0. While the cost-benefit assessment process under AMNOG (the German Pharmaceuticals Market Reorganization Act) has not been widely initiated by health insurance funds or the pharmaceutical industry since its introduction in 2011, ongoing updates to IQWiG's methodologies indicate that the process may continue to evolve, enhancing its role in future health technology assessments.

10.4 Recommendation

Since the introduction of the AMNOG procedure in 2011, neither the health insurance funds nor the industry have initiated a cost-benefit assessment, meaning the G-BA has not yet tasked IQWiG with conducting a KNB under section 35b SGB V. This may be due to the complexity of the process, which can take several years. However, the topic should continue to be monitored, as the IQWiG has updated its methodology and is actively working on this area.

11. Impact of the German benefit assessment on reimbursement and pricing

Authors: Susanne HUSCHENS, Almuth MARX, Kati STERNBERG

11.1 Abstract

This section discusses recent adjustments to Germany's drug pricing and reimbursement regulations, specifically within the context of the GKV-FinStG (2022) and the Medical Research Act (2025). It outlines the introduction of new pricing guardrails, including the calculation of price premiums or discounts based on the added benefit rating of medicines, and the impact of these regulations on price negotiations. The section details the implementation of a 20% combination discount for patent-protected drugs used in G-BA-designated combinations and the lowering of the annual revenue threshold for orphan drugs from €50 million to €30 million. It also highlights the introduction of the Medical Research Act, which aims to incentivize participation in clinical trials conducted in Germany by offering flexibility in reimbursement negotiations for drugs with substantial German patient involvement. The section concludes with recommendations for pharmaceutical companies, emphasizing the importance of aligning clinical trials with AMNOG requirements to avoid restrictions on negotiation flexibility, and the need to increase German patient participation in global clinical trials to overcome regulatory challenges.

11.2 Introduction

Irrespective of the outcome of the benefit assessment and with the exception of a few "lifestyle drugs", all prescription drugs are usually reimbursed in Germany. While the price should primarily depend on the added benefit and the costs in the indication, there have been two recent adjustments to the regulatory framework. The first introduced stricter restrictions in 2023, which are still not fully implemented, while the second partially suspended them in January 2024 as an "investment and research incentive" for drugs with a high participation of German patients during the clinical trial programme.

11.3 AMNOG-Guardrails

New pricing guardrails for price negotiations were introduced under the GKV-FinStG in 2022.

Previously, the price premium for a medicinal product was based on the added benefit rating (non-quantifiable, minor, considerable, or major added benefit) relative to the appropriate comparator therapy. This approach has now changed.

Under the new guardrails, the negotiated price of the comparator depends on whether it is patent-protected or off-patent, whether it has undergone AMNOG assessment, and the actual added benefit rating (see Table 1).

Table 4: ANMOG guardrails according to GKV-FinStG

Added benefit rating by G-BA	Characteristics of ACT[1] (in case of multiple ACT elements, most economical ACT is relevant)		Considered price of ACT for negotiations	Price potential of product vs. Considered ACT price
No benefit	Patent-protected	AMNOG-assessed	Actual price	At least 10% discount vs. ACT
		Not AMNOG-assessed	Actual price – 15%	
	Off-patent		Actual price	Best price parity vs. ACT[2]
Minor/non-quantifiable benefit	Patent-protected	AMNOG-assessed	Actual price	Best price parity vs. ACT
		Not AMNOG-assessed	Actual price – 15%	
	Off-patent		Actual price	Premium vs. ACT
Considerable/ major benefit	Patent-protected	AMNOG-assessed	Actual price	Premium vs. ACT
		Not AMNOG-assessed	Actual price – 15%	
	Off-patent		Actual price	

[1]ATC: Appropriate comparator therapy
[2]Deviations from the limit may be made in justified individual cases

11.4 Combination discount

As part of the GKV-FinStG, which took effect at the end of November 2022, a 20% combination discount was introduced in accordance with Section 35a Article 1 (1d) and 130e SGB V. This discount applies to all new medicinal products with patent-protected active ingredients used in GBA-designated combinations, as per Section 35a (3) sentence 4 SGB V, and dispensed at the expense of health insurance companies from May 2, 2023. The discount is calculated as 20% of the pharmaceutical company's selling price, excluding VAT (Bundesanzeiger, 2022).

The discount applies if the G-BA determines that the added benefit is not at least considerable, as per Section 35a (1d) sentence 1 SGB V. However, no deduction is made if a benefit assessment procedure is still pending. In this procedure, the G-BA will evaluate the potential for using new active ingredients in combination therapy for the indicated condition based on the pharmaceutical product's marketing authorization.

11.5 Lowering of annual revenue threshhold for Orphan drugs

Under the new law, the revenue threshold for orphan drugs has been reduced from €50 million to €30 million. As a result, medications generating more than €30 million in sales over a 12-month period will no longer be assessed as Orphan Drugs, thus will not receive the associated automatically attested added benefit. Note that this classification is independent of the EMA classification. These drugs will now require a comparison to an ACT defined by the G-BA, along with the submission of dossiers demonstrating that they offer a superior benefit over the ACT.

11.6 Current development – Medical Research Act 2025

The Medical Research Act, introduced in January 2025, aims to enhance Germany's attractiveness for clinical trials by reducing regulatory barriers and optimizing the framework for medical research. While the GKV-FinStG focuses on controlling drug prices and ensuring financial stability with strict pricing guardrails, the Medical Research Act seeks to foster long-term improvements in medical care and innovation.

For drugs with meaningful clinical trials conducted in Germany, the Act reinstates flexibility in reimbursement negotiations by lifting certain GKV-FinStG guardrails under specific conditions:

- **Participation:** At least 5% of study participants must be from Germany.
- **Compliance:** Trials must comply with Article 2(2) No. 2 of EU Regulation 536/2014 (non-interventional studies are excluded).
- **Verification:** The G-BA will assess and publish whether the criteria are met during the benefit assessment.
- **Validity:** The exemption lasts for three years, unless the company provides evidence of ongoing research in Germany.
- **Enforcement:** Without proof of ongoing research, the GKV-SV must terminate the existing agreement and negotiate a new one under the guardrails.

This policy reintroduces flexibility in reimbursement negotiations for drugs extensively tested in Germany, provided they meet the outlined criteria, balancing a robust research environment with financial oversight.

11.7 Recommendation

The guardrails of the GKV-FinStG pose significant challenges for pharmaceuticals with “no added benefit”, “minor added benefit” or low-cost ACTs. A considerable or major added benefit rating is crucial to avoid limiting negotiation flexibility from the outset, and this should be factored into the planning phase of clinical trials. Evaluating subpopulations—often used as a workaround when study populations don’t fully meet AMNOG requirements—will likely reduce the likelihood of achieving a considerable or major added benefit due to power loss. Therefore, every effort should be made to ensure clinical trials align with AMNOG requirements.

If a study design fully compliant with AMNOG is not feasible, increasing the participation of German patients and study centers in the global clinical trial program can help overcome the guardrails.

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Appendix

Appendix for Introduction to the classifying added benefit in the German HTA

Basis for classifying added benefit (based on G-BA Rules of Procedure (G-BA, 2008))

Categories of added benefit	Basis for the categories
The added benefit against to ACT is graded in ascending order:	
Less benefit / Harm	The benefit of the medicinal product to be assessed is smaller than the benefit of the ACT
No added benefit	No added benefit has been demonstrated
Non-quantifiable added benefit	Because the scientific data basis does not allow it
Minor added benefit	A moderate and not just small improvement of the therapy-relevant benefit that was previously unattained compared to the ACT
Considerable added benefit	A significant improvement of the therapy-relevant benefit that was previously unattained compared to the ACT
Major added benefit	A sustained improvement of the therapy-relevant benefit that was previously unattained compared to the ACT

Certainty of conclusion on added benefit

Categories of added benefit	Basis for the categories
In addition, the probability or certainty of the added benefit is assessed:	
Hint	Hint (weakest certainty of conclusions): meta-analysis demonstrating a homogeneous and statistically significant effect or multiple studies demonstrating clear treatment effects in the same direction, both with low qualitative certainty of results; individual studies demonstrating moderate treatment effects in the same direction with moderate qualitative certainty of the results; a single study demonstrating a statistically significant effect with moderate qualitative certainty of the results.
Indication	Indication (medium certainty of conclusions): meta-analysis demonstrating a homogenous and statistically significant effect or multiple studies demonstrating clear treatment effects in the same direction, both with moderate qualitative certainty of the results; individual studies demonstrating moderate treatment effects in the same direction with high qualitative certainty of the results; a single study demonstrating a statistically significant effect with high qualitative certainty of the results.
Proof	Proof (highest certainty of conclusions): meta-analysis demonstrating a homogeneous and statistically significant effect with high qualitative certainty of the results; at least two independent studies demonstrating clear treatment effects in the same direction with high qualitative certainty of the results.

Appendix for Chapter 5. Actuality of data cuts in German HTA – Examples

Benefit assessment of Nivolumab (Urothelial carcinoma, PD-L1 expression ≥ 1%, adjuvant therapy)

Nivolumab	
G-BA decision	20.10.2022
General information	Urothelial carcinoma; Limited until 15.12.2025
No data on overall survival presented	
Rationale of the pharmaceutical company	The first interim analysis (2nd data cut-off February 2021) for overall survival is linked to the interim analysis for the primary endpoint of disease-free survival (DFS) and depends on the achievement of the planned number of DFS events. As the specified significance level was not reached for the first interim analysis, the data on overall survival were not unblinded for the pharmaceutical company.
IQWiG/G-BA Assessment	The fact that the data on overall survival was not unblinded is not fully comprehensible, as at least for the 1st data cut-off (August 2020) - information on the number of deceased patients unblinded per treatment arm is available from the analyses on side effects in the study report. In addition, "death from any cause (without prior recurrence)" is also included as an event in the analyses of disease-free survival. disease-free survival, for which unblinded data per treatment arm is available.
Result	G-BA decision limited: final data cut-off for overall survival
Source: Nutzenbewertungsverfahren zum Wirkstoff Nivolumab (Neues Anwendungsgebiet: Urothelkarzinom, PD-L1-Expression ≥ 1 %, adjuvante Therapie) - Gemeinsamer Bundesausschuss	

Benefit assessment of Atezolizumab (Non-small cell lung cancer, PD-L1 expression ≥ 50 % of TC, EGFR/ALK-negative, adjuvant therapy after resection and chemotherapy)

Atezolizumab	
G-BA decision	05.01.2023
General information	Lung carcinoma, non-small cell; Limited until 01.10.2024
No consideration of the submitted DFS data from the 1st data cut	
Rationale of the pharmaceutical company	The pharmaceutical company submits analyses exclusively for the 1st data cut-off from January 2021. This only cover approx. 70% of the observation period of the IMpower010 study. Although data with a higher information content are available for the 2nd data cut-off due to the longer observation period, these are not presented by the pharmaceutical company either in the dossier or in the commenting procedure. The pharmaceutical company argues that two pre-specified analyses of the DFS will be performed: The interim analysis in January 2021 and the final analysis expected at the end of 2023. From the perspective of the pharmaceutical company, it would not be possible to analyse the DFS for the 2nd data cut-off in order to comply with international standards and guidelines on good clinical practice. In addition, he states that the interim analysis already forms the basis for the European marketing authorisation and is therefore sufficient from the perspective of the pharmaceutical company.

IQWiG/G-BA Assessment	This approach of the pharmaceutical company is not followed. In principle, according to the dossier template, corresponding analyses for all patient-relevant outcomes are to be submitted for the data sections presented, even if a data section was originally only planned for the analysis of individual outcomes. Therefore, the criticism of the pharmaceutical company's approach remains even after completion of the commenting procedure and it is concluded that the analyses on morbidity from the IMpower010 study presented by the pharmaceutical company are not usable for the benefit assessment.
Result	Limitation: pre-specified final analysis of disease-free survival
Source: Nutzenbewertungsverfahren zum Wirkstoff Atezolizumab (Neues Anwendungsgebiet: Nicht-kleinzelliges Lungenkarzinom, PD-L1 Expression ≥ 50 %, adjuvante Therapie nach Resektion und Chemotherapie) - Gemeinsamer Bundesausschuss	

Benefit assessment of Palbociclib (Breast cancer)

Palbociclib	
G-BA decision	15.12.2022
General information	Breast cancer; Re-assessment patient population a1
No consideration of the data as a whole (incomplete content)	
Rationale of the pharmaceutical company	-
IQWiG/G-BA Assessment	Benefit assessment after deadline with final study results of the PALOMA-2 study on all endpoints With regard to the data on quality of life and morbidity, the pharmaceutical company did not comply with this Only submitted analyses on the unplanned second data cut-off from 31 May 2017, but not on the more recent third data cut-off from 15 November 2021, which was also was pre-specified (final analysis of overall survival) The data on quality of life and morbidity from the PALOMA-4 study are not meaningful on their own Thus, the presented analyses on quality of life and morbidity from the PALOMA-2 study are not usable for the benefit assessment and the presented study results for the PALOMA-2 study are incomplete in terms of content Due to the fact that no assessable data on effects on quality of life are available, it is in particular not possible to assess the extent to which the increase in significant adverse events (CTCAE ≥ grade 3) caused by palbociclib corresponds to changes in quality of life compared to the control group.
Result	For these reasons, the G-BA determines that the preparation of the pharmaceutical company's data presented here does not meet the requirements and proves to be so incomplete that it prevents a sufficiently reliable and appropriate assessment of the added benefit. As a result, the G-BA determines that an added benefit has not been proven.
Source: Nutzenbewertungsverfahren zum Wirkstoff Palbociclib (Neubewertung nach Fristablauf: Mammakarzinom, Patientenpopulation a1) - Gemeinsamer Bundesausschuss	

Appendix for Capter 7. Appropriate comparator therapy (ACT)

Types of ACT with corresponding examples

Standard Options for ACT	
Category	**Example***
Single Comparator = a defined therapy of one substance or product → Single comparator studies are suitable for benefit assessment	INN: Patiromer Indication: Hyperkalemia (Metabolic Diseases) Patient Population: Children and adolescents aged 12 years and older with hyperkalaemia → ACT: Polystyrenesulfonates (CaPSS, NaPSS)
Several "equally appropriate" Comparators = multiple substances or products are defined with an "OR" linkage in between → Single comparator studies are suitable for benefit assessment If several alternatives for the comparator therapy are equally appropriate, the additional benefit can be demonstrated compared to one of these therapies.	INN: Pembrolizumab Indication: Adenocarcinoma of the stomach or gastroesophageal junction (Oncology) Patient Population: Adults with locally advanced, unresectable or metastatic HER2-positive adenocarcinoma of the stomach or gastroesophageal junction with PD-L1-expressing tumours (CPS ≥ 1); first-line therapy →ACT (of Pembrolizumab in combination with trastuzumab and fluoropyrimidine- and platinum-based chemotherapy): Trastuzumab in combination with capecitabine and cisplatin OR Trastuzumab in combination with 5-fluorouracil and cisplatin
Therapy according to doctor's choice → Multi comparator studies might be needed for benefit assessment depending on which products are considered to be according to doctor's choice	INN: Nirmatrelvir / Ritonavir Indication: COVID-19 (Infectious Diseases) Patient Population: Adults with COVID-19, who don't need oxygen and have a high risk to develop severe COVID-19 progression ACT: Therapy according to doctor's choice
Patient-individual therapy → Multi comparator studies might be needed for benefit assessment depending on which products are considered to be appropriate for the patients	INN: Axicabtagen-Ciloleucel Indication: Follicular lymphoma (Oncology) Patient Population: Adults with follicular lymphoma after 3 or more systemic therapies → ACT: Patient-individualised therapy with selection of: • Bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy in accordance with the marketing authorisation, • Lenalidomide + rituximab, • Rituximab monotherapy, • Mosunetuzumab, • Tisagenlecleucel • considering the previous therapy, the course of the disease and the patient´s general condition.

Patientenindividuelle Therapie unter Berücksichtigung von A B C Results in multiple comparator study	Patient population of the benefit assessment and ACT Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who show a response (complete or partial) after completion of platinum-based first-line chemotherapy, maintenance therapy ACT for Rucaparib (Rubraca) as monotherapy: A patient-individualised therapy with a choice of: – Bevacizumab – Olaparib – Niraparib – Olaparib in combination with bevacizumab <u>considering</u> – the previous therapy – the presence of a BRCA 1/2 mutation – the presence of genomic instability Status of the information: October 2023 [Source: Nutzenbewertungsverfahren zum Wirkstoff Rucaparib (Neues Anwendungsgebiet: Ovarialkarzinom, Eileiterkarzinom oder primäres Peritonealkarzinom, Erhaltungstherapie nach Erstlinientherapie) - Gemeinsamer Bundesausschuss (g-ba.de)]
Off Label use	
<u>Off-Label ACT</u> = a Marketing Authorization is not mandatory for products to be declared as ACT	
No Standard Options for ACT	
<u>Best-Supportive-Care (BSC)</u> = no relevant therapeutic alternatives, patient-specific approach in the sense of optimised, supportive treatment (multi comparator)	CAVEAT: BSC does not mean „just“ Placebo control. The concomitant therapy should be clearly described within the study protocol and should reflect supportive therapy used in Germany.
Observational waiting	
*The ACTs described reflect the state of the time	

Overview of the case studies

Active substance	Name	Indication	Therapeutic area	ACT change (reason)	ACT (defined by G-BA)	Comment
Fluticasonfuroat/ Umeclidinium/ Vilanterol	Trelegy Ellipta	Chronic obstructive pulmonary disease (COPD)	Respiratory system diseases	Before dossier submission / Update of guideline à Study was no longer suitable for deriving the added benefit	Patient-specific therapy optimisation - considering previous therapy.	Several ACT changes during an ongoing study
Ertugliflozin	Steglatro	Diabetes mellitus Typ 2	Metabolic diseases	n.d. (laut AMNOG Monitor, checken im Beschluss)	Patient-specific therapy considering the patient-specific therapy goal.	ACT change shortly before dossier submission
Mepolizumab	Nucala	Rhinosinusitis	Respiratory system diseases	New scientific knowledge	Dupilumab or omalizumab, each in combination with intranasal corticosteroids (budesonide or mometasone furoate).	ACT change in the current procedure (during/after commenting process)
Baricitinib	Olumiant	Atopic dermatitis	Skin diseases	Written statement process à Two study populations were combined into one (Subpopulation A then had the same ACT as B)	Dupilumab	ACT change as a result of a G-BA decision
Tucatinib	Tukysa	Breast carcinoma	Oncological diseases	Change after written statements of the manufacturer and medical societies à Clinical trail from the dossier was accepted after all and reassessed by IQWiG	Treatment as directed by the physician.	Consideration of a study as a result of an amendment / consideration by IQWiG addendum without new benefit assessment
Nivolumab	Opdivo	Melanoma	Oncological diseases	During written statement process, ACT change following updated guideline	Vemurafenib or Vemurafenib plus Cobimetinib or Dabrafenib plus Trametinib | Nivolumab or Pembrolizumab | patient-specific therapy	Non-consideration of a study because of an ACT change

Risankizumab	Skin diseases	Plaque psoriasis	Skin diseases	Fumaric acid esters no longer an option in the appropriate comparator therapy	Adalimumab or Guselkumab or Ixekizumab or Secukinumab|Adalimumab or Brodalumab or Guselkumab or Infliximab or Ixekizumab or Secukinumab or Ustekinumab	Non-consideration of a study conducted for AMNOG as a result of an ACT change
Dostarlimab	Jemperli	Endometrial cancer	Oncological diseases	During written statement process, Paclitaxel was added, but the data shown by the manufacturer were not suitable for deriving an added benefit regardless of the zVT, therefore no new benefit assessment was required	Therapy according to physician´s choice	ACT change without IQWiG addendum and without new benefit assessment
Ozanimod	Zeposia	Multiple sclerosis	Nervous system diseases	After written statement process	Interferon beta-1a or Interferon beta-1b or Glatiramer acetate or Ocrelizumab, considering the marketing authorisation. | Alemtuzumab or Fingolimod or Natalizumab	ACT change with a limited G-BA decision of 6 months / Possibility of avoiding re-assessment
Ponesimod	Ponvory	Multiple sclerosis	Nervous system diseases	RCT against Teriflunomid, which was not ACT until commenting process à reassessment by IQWiG after change of ACT	Interferon beta-1a or interferon beta-1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab	Suspension of the G-BA decision for 6 months due to an ACT change (due to updated guideline)

Idecabtagen vicleucel	Abecma	Multiples Myelom	Oncological diseases	Shortly before submission of the dossier, the G-BA divided the patient population into two subgroups and adapted the active substances to the patient-specific therapy. The study shown in the dossier was therefore no longer suitable for benefit assessment.	Patient-specific therapy	G-BA decision still pending