The Challenges of Comparative Routine Practice Data Collection (AbD) for Early Benefit Assessment (AMNOG)

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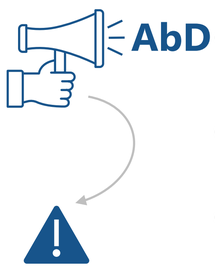
INTRODUCTION

For an increasing number of medicinal products, **randomized controlled trials** are **not feasible or ethically defensible** (e.g. ATMPs & orphan drugs).

To **close the evidence gap**, the German Federal Joint Committee (G-BA) can demand a post-launch study: **Routine practice data collection** (**AbD**) and analysis.



- Conditional market authorization (MA)
- MA under exceptional circumstances
- Rare diseases (orphan disease)

AbD aims to generate **comparative evidence** against the local standard of care for clinical assessment.

Challenges

Rigorous **methodological requirements** of HTA within strictly **defined timelines**.

METHODS

Systematic review and comparison of available AbD documents to identify challenges and requirements of the process:

- Review of publicly available documents of **all AbD procedures** initiated by G-BA.
- Design of a **process roadmap** by combining publication dates with G-BA's set deadlines
- Comparison of **methodological requirements** for AbD with decisions of **AbD procedures**.

CONCLUSION

With AbD, the G-BA imposes strict requirements to generate real-world evidence for HTA. Extensive adjustments to existing registries are required prior to data collection.

Going forward, the quality and quantity of real-world data, and their relevance for HTA, are likely to improve. This will enhance the overall evidence base for healthcare decision-making.

RESULTS

BY OCTOBER 9TH 2023, 10 ABD PROCEDURES WERE INITIATED BY G-BA.

ID	Active ingredient (trade name), disease	IQWiG AbD concept	Stakeholder participation process	Decision on requirement	Study documents (any version)
1	**Onase-Vec (Zolgensma)**, Spinal muscle atrophy	✓	✓	✓	✓*
2	**Risdiplam (Evrysdi)**, Spinal muscle atrophy	✓	✓	✓	⌛**
3	**Brexu-Cel (Tecartus)**, Mantel cell lymphoma	✓	✓	✓	✓
4	**Fedratinib (Inrebic)**, Myelofibrosis	✓	✓	✓	✗***
5	**Val-Rox (Roctavian)**, Hemophilia A	✓	✓	✓	✓
6	**Etrana-Dez (Hemgenix)**, Hemophilia B	✓	✓	✓	⌛
7	**Brexu-Cel (Tecartus)**, Acute lymphobl. Leukemia	✓	✓	✓****	✗****
8	**Exa-Cel**, Sickle cell disease	⌛	⌛	⌛	⌛
9	**Exa-Cel**, Beta-Thalassemia	⌛	⌛	⌛	⌛
10	**Fida-Vec**, Hemophilia B	⌛	⌛	⌛	⌛

* SAP not publicly available; ** process paused in anticipation of an extended indication; *** not handed in by sponsor, process stopped; **** process stopped by G-BA due to infeasiblility caused by small patient numbers; ✗ not submitted; ✓ submitted; ⌛ pending

Table 1: Status of publicly available documentation of current AbD procedures (October 9th 2023)

The G-BA publishes AbD related documents, such as formal decisions with main justifications, a transcript of the oral expert hearing, as well as the study protocol and SAP on its website as each procedural step is completed (Tab. 1).

Two AbD procedures have started data collection, one was terminated because no study documents have been submitted, and one was discontinued due to a lack of feasibility.

Currently, six AbD procedures are in consultation or under evaluation.

THE PROCEDURAL TIMELINES PRIOR TO THE START OF AN ABD HAVE BECOME MORE PREDICTABLE OVER TIME, BUT THERE ARE STILL UNCERTAINTIES.

The AbD process is governed by the G-BA's Rules of Procedure (Verfahrensordnung). However, certain timelines were only specified after the initiation and progression of several AbD procedures (e.g. in April 2023).

Still, some procedural steps lack defined durations. For example, the time to prepare the AbD concept (due within six months after the initiation of a AbD procedure) varies greatly within the first AbD procedures, but tends to become shorter (3 months) (Fig. 1).

For the most advanced procedures, an additional (2nd) revision of study documents was necessary to implement the changes requested by G-BA and IQWiG. Fig. 2 shows a exemplary timeline of procedurals steps.

After the AbD has started, the G-BA requires regular status updates and interim analyses that can result in a stop due to futility. Once the AbD is completed the G-BA re-assesses the additional benefit.

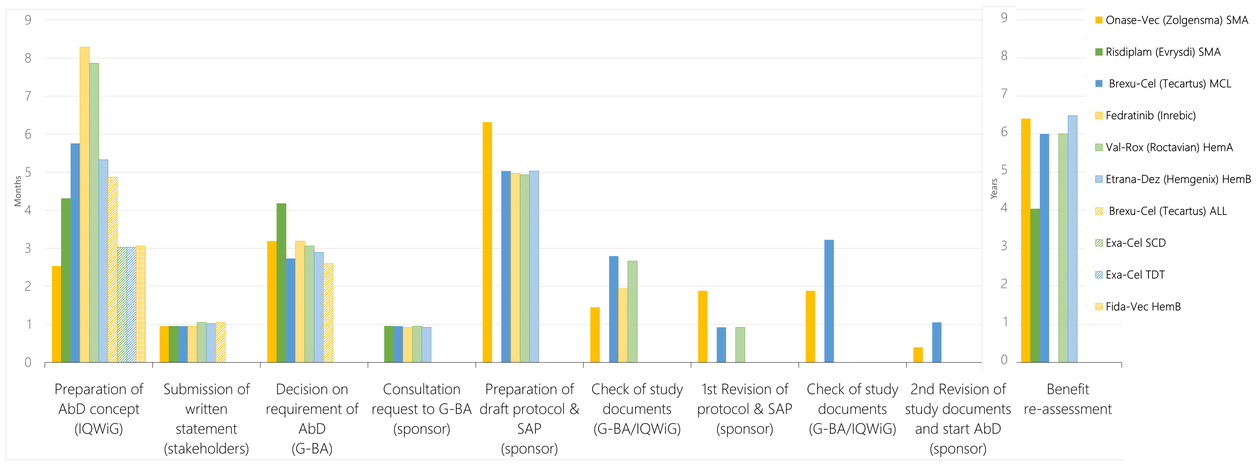


Figure 1: Duration of procedural steps of current AbD processes, timelines set by G-BA (October 9th 2023)

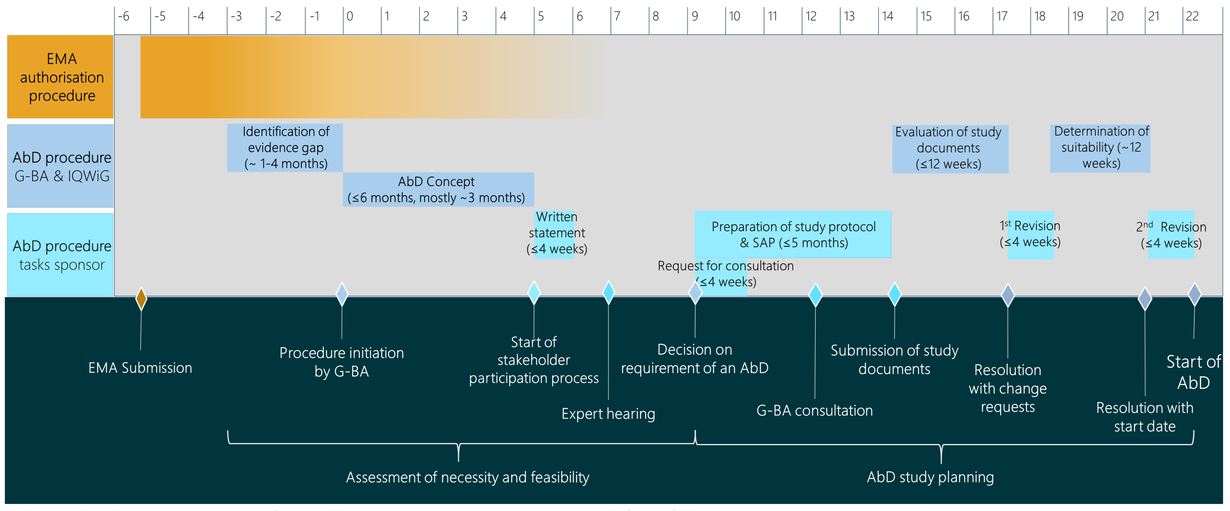


Figure 2: Process roadmap for AbD preparation based on G-BA Rules of Procedure and current AbD procedures

KEY CHALLENGES IN THE ABD PROCESS IN RELATION TO THE PICOS FRAMEWORK: (1) CHANGES IN THE PATIENT REGISTRIES, (2) SAMPLE SIZE, AND (3) TARGET TRIAL DESIGN

Population	Comparator	Outcome
• Population defined in AbD differs from the definition in the marketing authorisation Label 2/7 • Population expanded after extension of marketing authorisation for patients < 2 months 1/7	• Discussion on positivity (i.e., patients being suited for treatment with the comparator and intervention, and all comparators being represented in the registry) 6/7 • Comparator added after stakeholder participation process 1/7 • Comparator added after start of AbD 1/7	• Registry lacks of instruments for QoL measurements 5/7 • Approximation of SAE by AE leading to hospitalization/death 2/7 • Collection of health related quality of life data no longer required 1/7

Study	
• Registry	Major adaptations required to ensure data quality 7/7 Delayed data entry from centres to registry 3/7 Increase in individual patient reports to the registry necessary 2/7
• Follow-up time	At least 36 months 6/7 At least 24 months 1/7
• PRO Collection	Registry needs to measure PROs at fixed timepoints 4/7
• Sample Size	Integration of european registries suggested to increase low sample sizes in Germany 4/7 Recruitment ratio unclear (e.g. due to variations in endpoint assumptions) 3/7 High uncertainty of effect sizes 2/7 AbD stopped due to insufficient number of patients 1/7
• ITT principle	Definition of baseline and start of observation complicated; Dealing with bridging by comparator 4/7

Table 2: Critical aspects regarding P(I)COS criteria from 7 AbD procedures with published IQWiG concepts

AbD within registries require major adaptations to the workflow and data entry to ensure data quality and completeness (Tab. 2). Changes to registries included PRO integration, AE documentation revisions, and comprehensive endpoint collection. Study design challenges arose due to limited empirical evidence on effect sizes, leading to sample size variation. New comparators were added during or after AbD preparation.

Despite specific challenges, common obstacles were observed in most processes.

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REFERENCES

G-BA's Rules of Procedure https://www.g-ba.de/richtlinien/42/ (German)
AbD procedures https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/ (German)
General AbD Concept https://www.iqwig.de/en/projects/a19-43.html (English)

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