vfa. Die forschenden Pharma-Unternehmen
Research-Based Pharmaceutical Companies

Position paper - AMNOG 2025

Special treatment settings need special assessment

New therapies are increasingly tailored to meet the needs of smaller patient populations. Randomized controlled trials (RCTs) are not always feasible in this context for practical and ethical reasons. This evolution needs to be addressed in the assessment of the additional benefit of new medicines (AMNOG), to avoid a disconnect between requirements and scientific progress in drug development. Special treatment settings where studies at the highest evidence level are impossible or inappropriate therefore require special status and adapted methods in the AMNOG process.

Research means change

Therapeutic options emerging in recent years have become increasingly targeted to narrowly defined, smaller groups of affected patients. Scientific progress is becoming a challenge for drug approval, which is traditionally based on the conduct of randomized controlled trials (RCTs). Although RCTs are considered the gold standard for typical cases, they are not always practically feasible or ethically justifiable. For this reason, alternative investigational approaches are being developed and applied, such as single-arm studies without a control arm or with historical control groups.

Regulatory authorities have been adapting to this trend for years. Whether RCTs are necessary and feasible, or whether alternative study approaches can be chosen, is assessed specifically for each approval. The focus is on case-by-case evaluation that balances timely availability of an effective and safe drug against the expectation of getting the highest possible certainty of study results. This weighing-up process considers factors such as the nature, severity, and rarity of the disease, the unmet medical need, and the associated ethical aspects. Especially when there are early indications in drug development that patients will benefit significantly from the new therapy, there is a need for timely treatment access based on non-randomized data.

Flaw in the AMNOG process

There are significant discrepancies in the handling of non-randomized data in the AMNOG process. The legal framework of AMNOG benefit assessment recognizes in the Ordinance for the Benefit Assessment of Medicinal Products (AM-NutzenV) that there are therapeutic settings in which it is "*impossible or inappropriate to conduct or demand studies at the highest level of evidence*." In this case, "*best available evidence must be submitted*."

However, this provision is never implemented in practice as the possibility and the appropriateness of conducting clinical trials at the highest evidence level (i.e., RCTs) is not systematically reviewed and submitted lower-evidence-level studies are routinely deemed unusable (e.g., due to a single-arm study design). In other words, the unique features of particular treatment situations are not adequately addressed.

This has been an inherent flaw in AMNOG since its inception in 2011, and has in fact been magnified by the recent SHI Financial Stabilization Act (GKV-FinStG). The consequences are becoming increasingly apparent. Additional clinical benefit is not given due recognition, with the result that the treatments concerned do not meet the criteria for fair and reasonable reimbursement. This can have a detrimental impact on the availability of new treatments in the care of patients.

Review of the highest-level-evidence requirement must be routine

AMNOG benefit assessment must include routine review of whether it is impossible or inappropriate to conduct or demand studies at the highest level of evidence, or whether the highest feasible level of evidence is already available. Insights from drug development and scientific advice in the context of marketing authorization should serve as the basis for this review, which should take place as early as possible and involve the regulatory authorities and, if necessary, experts from academia and clinical practice. The review criteria should reflect the specific features of the treatment situations and clinical care, in particular including unmet medical need, disease severity, and size of the target population.

Special status in the assessment process

If the review determines that it is impossible or inappropriate to conduct or require studies satisfying the highest level of evidence, then a special treatment setting is involved. And special treatment settings merit special treatment in the benefit assessment process. The best available evidence must be used for the assessment. Assessment should then proceed, taking into account the lower level of result certainty and using adapted methods to assess studies below the highest level of evidence.

Establishment of adapted methods

For assessments involving these special treatment settings, G-BA should establish adapted, workable methods for assessment of studies below the highest level of evidence, in collaboration with the relevant stakeholders. This would include establishing criteria for the use of external controls and workable methods for identifying and adjusting confounders, as well as for the acceptability of surrogate endpoints. These criteria should enable assessment on the basis of adapted requirements in terms of result certainty. Real world data can also be useful, for example to depict natural disease history or use the current standard of care as a basis for comparison. Despite advances in the quality of disease registries, registry data has not been accepted to date.

Conclusion

The AMNOG process needs to be made fit for medical progress. This entails creating a future-proof framework for benefit assessment involving special treatment settings where RCTs are impossible or inappropriate. Otherwise, Germany risks falling further behind on scientific progress and permanent loss of its European leadership in giving patients access to innovative medicines.

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