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Leveraging Health Technology Assessment (HTA) for Market Access
A Statistical Programming Perspective on German HTA Submission

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ABSTRACT

Health Technology Assessment (HTA) in European countries is an essential process that goes beyond regulatory approval by assessing a drug's real-world value. While regulatory submissions focus on proving safety and efficacy, HTA evaluates additional factors to guide pricing, patient access, and reimbursement decisions. In Germany, the Gemeinsamer Bundesausschuss (G-BA) leads the HTA process, using clinical evidence—including Patient-reported outcomes (PRO), such as quality of life (QoL), safety, and efficacy—to establish a drug's value proposition. Demonstrating significant benefits in these areas can result in favorable pricing and improved revenue outcomes, making HTA a key determinant of successful market access. To ensure patient access to innovative therapies, securing broad reimbursement coverage for specific patient subgroups is essential. After regulatory approval, engaging in proactive negotiations with HTA agencies can facilitate reimbursement, ensuring that patients in need receive timely and equitable access to necessary treatments.

In this paper, we will share our experience as statistical programmers in preparing the reports for a German HTA application to the G-BA, which contributed to a successful outcome. We will compare regulatory submissions with German HTA submissions, highlighting their key differences.

INTRODUCTION

HTA in Germany, led by the G-BA, plays a crucial role in evaluating drugs beyond regulatory requirements, focusing on real-world value including QoL, safety, and efficacy. Pharmaceutical companies must submit a dossier to the G-BA no later than their product launch in Germany. This dossier, based on authorization documents and all studies conducted on the medicinal product, aims to validate the claim of any additional benefit over the appropriate comparator and achieve the best possible resolution on the benefit assessment from G-BA.

Approval categories	Details
Major Benefit	The drug is recognized to have an added benefit over the current standard of care without any restrictions.
Considerable Benefit	The drug is recognized to have an added benefit, but only for a specific subgroup of patients or under certain conditions.
Minor Benefit	The drug is assessed to have minor additional benefits compared to the current standard of care.
Non-quantifiable added Benefit	The added benefit of the drug cannot be quantified due to insufficient data or other reasons.
No Added Benefit	The drug is considered to offer no improvement over the standard treatment and may be subject to price restrictions.

Table 1. Categories of G-BA-HTA approval

The different categories of G-BA resolutions typically include ones listed in Table 1 above, ordered from best case to worst case. A greater level of additional benefit leads to more advantageous price negotiations, broader coverage, and better reimbursement, ultimately enhancing patient access.

MAIN DIFFERENCES BETWEEN G-BA HTA DOSSIER & CSR

A Clinical Study Report (CSR) is an essential component of regulatory submission to agencies such as the US FDA and the European Medicines Agency (EMA). It provides detailed results from clinical trials and is crucial for obtaining approval to bring new treatments to patients. In contrast, the HTA Dossier is submitted to relevant agencies in countries with pricing and reimbursement processes that depend on recommendations from Health Technology Assessment (HTA) agencies, such as the G-BA in Germany and the National Institute for Health and Care Excellence (NICE) in the UK.

Table 2 lists some key differences between G-BA-HTA dossier related outputs and Clinical Study Report (CSR) outputs for a typical regulatory submission and details on each in the sections below. **This list is based on the experience working on the Oncology trials at Servier.**

G-BA	CSR
1.HTA specific Analysis Plan	CSR specific SAP which is usually finalized before TLF programming commences
2. Datasets are not submitted	Regulatory submission needs to submit the datasets
3. Large number of outputs, mainly Table and Figures	A typical CSR usually has 150-200 outputs
4. Time to event analysis for Safety and related endpoints	No such analysis in the CSR
5. Patient reported outcomes (PRO) such as Quality of Life and related endpoints	PRO related outputs are not a focus of the CSR
6. Period of follow-up for efficacy, **QoL** and safety endpoints	No such analysis in the CSR
7. Completion rates of QoL	No such analysis in the CSR
8. Subgroup analysis for selected secondary and tertiary endpoints of interest. New Subgroups may be defined for HTA.	CSR only performed subgroup analysis for primary endpoint and key secondary endpoints.
9. Requires additional subpopulation analyses for reimbursement decisions, often beyond CSR scope.	Includes predefined subpopulation analyses per SAP for regulatory approval.

Table 2. G-BA-HTA vs CSR outputs

1. HTA ANALYSIS PLAN VS SAP

Unlike CSR submissions, where the SAP is finalized before initiating TLF programming, HTA analyses are exploratory, making the scope of work for a G-BA submission broader. It evolves based on the interpretation of interim results, requiring iterative analyses and adjustments throughout the process.

2. DATASETS

Regulatory submission requires the submission of Analysis dataset to support the submission. There is no such requirement for the G-BA-HTA submissions, only the outputs are submitted.

3. LARGE NUMBER OF OUTPUTS

G-BA HTA dossier can exceed 500+ Outputs, far exceeding 150-200 in a typical CSR because they include subgroup, sensitivity and post- hoc analyses, additional sub-populations, and data cut-offs.

4. TIME TO EVENT ANALYSIS FOR SAFETY AND RELATED ENDPOINTS

Time to event analysis for Adverse event outputs is part of the G-BA-HTA submission and requires an **analysis dataset (ADAETTE) to be created specifically for these endpoints**. For example, Time to any AE, first serious AE, first severe AE etc.

These outputs are important to G-BA because adverse events can impact both adherence to the drug and economics:

- The timing of adverse events affects treatment adherence and costs. A drug that causes severe events early on may be used less frequently in real-world settings compared to one with later or fewer adverse events.
- Time-to-adverse-event data helps estimate the long-term costs associated with adverse events, thereby shaping budget planning and cost-effectiveness models.

5. PATIENT REPORTED OUTCOMES AND RELATED ENDPOINTS

G-BA highly values QoL data from validated Patient-Reported Outcomes instruments (e.g., EQ-5D, EORTC QLQ-C30, FACT). They are used to assess the added benefit of a treatment – person's overall well-being, including their physical, mental, emotional, and social health and influence reimbursement decisions, shaping cost-effectiveness models and long-term healthcare planning.

Specifically, time to event analysis (including time to first worsening and time to first improvement) helps to determine how long patients maintain their quality of life before experiencing a decline. This analysis requires additional ADaM datasets that are not included in the CSR, such as ADQOLTTE or ADQSTTE based on QoL.

Besides Time to event analysis, Mixed Model for Repeated Measures (MMRM) analysis of the QOL endpoints is requested by G-BA HTA.

6. FOLLOW-UP PERIODS FOR EFFICACY, QOL AND SAFETY ENDPOINTS

Outputs for the follow-up periods for endpoint of QoL, Efficacy, and Safety help provide a clear view of **long-term treatment** to G-BA. These types of outputs are typically not included in CSR.

By including these follow-up analyses, the submission to G-BA becomes more compelling, offering a clearer justification for long-term treatment value in pricing, reimbursement, and market access discussions.

7. COMPLETION RATE OF QOL

QoL data are usually collected on scheduled visits. To ensure the reliability of QoL analyses (e.g. time to first worsening, change from baseline), we calculate proportion of subjects who completed the QoL questionnaire. We can refer to this proportion as the completion rate.

8. SUBGROUP ANALYSIS FOR SELECTED SECONDARY AND TERTIARY ENDPOINTS OF INTEREST

G-BA requires comprehensive subgroup analyses to help determine the patients who benefit most from the treatment. G-BA requests the following types of subgroups for analysis:

- Demographic Subgroups: Age, gender, and other demographic factors that may impact treatment efficacy or safety.
- Disease-related Subgroups: Different stages of the disease, baseline severity, or specific disease characteristics (e.g., tumor size or stage).
- Previous Treatment Subgroups: Patients with prior treatments or different lines of therapy, such as first-line vs. later-line treatments.
- Comorbidity Subgroups: Subgroups based on other health conditions or risk factors (e.g., seizure, cardiovascular disease, diabetes).
- Geographic Subgroups: In some cases, regional or country-specific analyses may be needed.
- Post-hoc subgroups due to the iterative nature of HTA analyses.

These subgroups help G-BA assess the treatment's real-world value across different patient populations, guiding reimbursement and market access decisions.

Treatment-by-subgroup interactions are used to analyze how the treatment effects vary across the subgroups.

9. ANALYSES OF SUBPOPULATION

G-BA requires subpopulation analysis to understand how a drug works for different patient groups. This ensures consistent benefits, supports reimbursement decisions, compares treatments, and provides evidence for tailored recommendations. They need specific analyses targeting designated subpopulations to demonstrate differential treatment effects, which are generally not required in CSR. For example, G-BA did not accept the protocol-defined definition of the appropriate candidates for non-intensive therapy for a trial, so a population subset was defined according to G-BA's requirements.

CONCLUSION

Statistical programmers play a crucial role in supporting HTA G-BA submissions by transforming CSR data into tailored analyses that meet G-BA’s specific requirements. This includes:

- Ensuring data consistency, accuracy, and alignment between CSR and G-BA-HTA outputs.
- Generating subgroup analyses and additional statistical outputs beyond standard CSR requirements.
- Collaborating closely with statisticians and stakeholders to refine methodologies and adapt outputs per G-BA’s expectations.

These efforts have helped Servier achieve ‘Major Added Benefit’ and ‘Considerable Added Benefit’ for its medicinal products in recent years. Link below in references from the AMNOG monitor for the G-BA resolutions.

REFERENCES

Resolutions from G-BA: https://www.amnog-monitor.com/procedures/resolutions/

Benefit assessment in Germany: implications for price discounts - PMC

Benefit Assessment of Medicinal Products - Gemeinsamer Bundesausschuss

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