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REIMBURSEMENT IN GERMANY: THE IMPACT OF THE FEDERAL JOINT COMMITTEE'S RECENTLY REVISED REQUIREMENTS FOR AMNOG DOSSIERS

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Abstract

In Germany, the Federal Joint Committee (G-BA) defines the requirements for the scientific evaluation of the benefits, the necessity and the economic efficiency of medicines to be reimbursed, in accordance with AMNOG (Arzneimittelmarkt-Neuordnungs-Gesetz). The requirements have been recently revised and were entered into force on 17 January 2019. For pharmaceutical companies, this means that the requirements for a reimbursement dossier have now changed. Our aim is to summarise and evaluate the potential impact of these important changes. Our summary focusses on the structure and contents of the AMNOG added benefit dossier (Dossier zur Nutzenbewertung gemäß §35a SGB V).

Updated: Benefit Assessment in Germany

The revised G-BA requirements offer simplifications regarding the preparation of clinical trial results, such that the effort for companies should be reduced. Simplifications and clarifications have been provided regarding the specification of the presentation of results on single studies, meta-analyses and subgroup analyses, effect modifications, indirect treatment comparisons, and the choice of the appropriate comparator. The instructions for the presentation of adverse events have been improved and criteria for their presentation at the level of research have been better specified. The updated requirements for reimbursement of medicines in Germany offer clearer instructions to pharmaceutical sponsors on how to develop reimbursement dossiers. Sponsors can potentially reduce the efforts required for the development and presentation of clinical trial results. They also have further opportunities to maximize their chances of a successful submission.

G-BA & Updates for AMNOG Dossiers

A selected list of updated requirements for German benefit assessment is provided in Table 1. Some of these updates reduce efforts for the reporting of results, others create additional efforts. In several places, specifications that often created ambiguities in the past have been specified more precisely.

Simplifications in terms of efforts and clarifications have been introduced particularly for subgroup analyses. Kaplan-Meier curves need only to be provided for subgroups with a significant treatment interaction, and the inclusion criteria for including subgroups in the analyses have been specified more precisely (>10 patients per subgroup, >10 events, see Table 1). The number of required analyses can be substantially reduced because results on AEs after SOC and PT only need to be presented if the respective outcome for the total population is statistically significant.

Effort-increasing updates refer to extended requirements for recherche on study data, the assessments into heterogeneity in meta analyses, the characterization of subpopulations and the use of more sophisticated methods (e.g. MMRM, see Table 1).

AMNOG topic	Updated contents	Chapter*
Recherche on study data	• "in-process & other non-indexed citations" are to be included in MEDLINE recherche • Information of G-BA websites are to be considered	4.2.3.2, 4.2.3.4
Meta analyses: I^2	• I^2 not recommended anymore for the assessment of heterogeneity between study data	4.2.5.3
Indirect comparisons	• Methods for testing homogeneity/heterogeneity among included studies need to be described	4.2.5.6, 4.3.2.1.2
Reporting results on 'Added benefit'	• If a benefit assessment involves more than one comparator, a statement on the added benefit should refer to the overall set of comparators	4.3
Studies of the pharmaceutical manufacturer	• Pharmaceutical manufacturers must specify whether data cuts of their studies are 'planned' or 'conducted'.	4.3.1.1.1
Study design and study populations	• A "characterization of the study population" is to be carried out also for subpopulations • Specifications regarding dropout rate, treatment discontinuation, treatment duration, observation period	4.3.1.2.1
Endpoints	• Specifications on incomplete observations and observation periods, use of Kaplan-Meier methods • Longitudinal analyses: explicit recommendation of MMRM (Mixed effect Repeated Measures) • Specifications on Adverse event (AE) analyses: ○ Total rate of AE, SAE, AEs of special interest ○ Discontinuations due to AEs ○ AEs differentiated by severity (e. g. CTCAE[1]), SOC[2], PT[3] according to MedDRA[4]	4.3.1.3.1
Subgroup analyses	• Only for variables with >10 patients in any of the subgroups of a subgroup variable • Binary outcomes: only if >10 events in at least one of the subgroups of a subgroup variable • Survival: Kaplan-Meier curves only for subgroups with significant interaction • Adverse event analyses: ○ Overall AE rates AESI, SMQs: present complete set of subgroup analyses ○ AEs by SOC and PT: subgroup analyses only if statistically significant for the total population	4.3.1.3.2

*Table 1 Selected list of updated requirements for German benefit assessment according to G-BA rules for procedures from 21.02.2019 [1] , Module 4, *ordered by chapter. Abbreviations: [1]CTCAE: Common Terminology Criteria for Adverse Events. [2]SOC: System Organ Class. [3]PT: Preferred Terms. [4]MedDRA: Medical Dictionary for Regulatory Activities.*

Find THE VALUE STORY easily – Watch it pop up

Confronted with digging through thousands of outputs to find a story of added benefit?

Not necessary – use Numerus's Interaction Explorer Board.

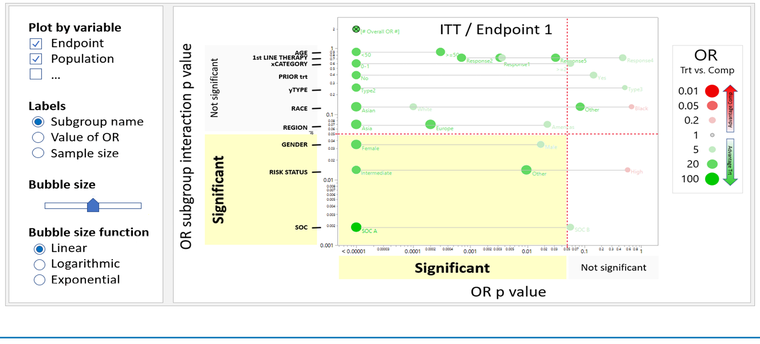
Numerus's Interaction Explorer Board helps identify treatment effects among subpopulations, subgroups and endpoints. The App is hierarchically structured such that treatment effects can be visually investigated, answering questions on added benefit from top-to-bottom:

- **Overall** treatment effects among subpopulations
  - Per **subpopulation**: treatment effects among endpoints
    - Per **endpoint**: treatment effects among **subgroups**

Numerus's Interaction Explorer Board can be interactively used and adapted to study-specific requirements and different data constellations and effect measures. Have a look, ask your question, and watch the answer pop up! – Contact bd@numerus.com.

Numerus's Interaction Explorer Board

Figure 1 **Numerus's Interaction Explorer Board** helps identify treatment effects among subpopulations, subgroups and endpoints. Effect sizes can be hierarchically visualized and adapted to answer specific questions. It detects risk factors and opportunities when searching for an added benefit and substantially reduces the efforts required for finding the story among hundreds or even thousands of analyses.



Conclusions

The G-BA has updated the requirements for the evaluation of health benefit assessment required in the framework of dossier submission. The updated requirements offer clearer instructions to pharmaceutical sponsors on how to develop reimbursement dossiers; they offer simplifications regarding the preparation of clinical trial results in many places, while increasing methodological efforts in other places.

Finding the health benefit story in the process of the preparation of a dossier sometimes requires digging through a set of hundreds or even thousands of outputs and results. This is a complex process that has usually to consider at least four dimensions: the level's subpopulations, endpoints, subgroups and effect measures. Numerus's Interaction Explorer Board helps identify effects among all these dimensions by means of a hierarchically structured visualization of treatment effects.

[1]Available from https://www.g-ba.de/downloads/40-268-4890/2019-02-21_VerfO_Aenderung-Anlage-I-II_Kapitel-5_Anlage-II-7_WZ.pdf?