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**Concepts for the generation of
routine practice data and
their analysis for the benefit
assessment of drugs according
to §35a Social Code Book V
(SGB V)¹**

Extract

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Executive summary

On 2 May 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) according to §139a (3) Social Code Book V (SGB V), to develop scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a SGB V.

Research question

The aims of this work are

- The creation of an overview of possible concepts for generating and analysing routine practice data. In particular, data collections that are not classified as randomized controlled trials (RCTs) should also be considered.
- The assessment of the identified concepts of data generation and their analysis with regard to their suitability to answer the research question of a benefit assessment according to §35a SGB V, especially with regard to the possibility of quantifying the added benefit of a new drug.
- The specification of criteria for data quality and the methodological requirements for the data collected within the framework of the respective generation of data. In this regard, the measures required to ensure data quality should also be addressed.
- The definition of requirements for reporting, as well as for the preparation and structure and the statistical analysis of the data collected within the framework of the respective generation of data.

Methods

Information retrieval and assessment

According to the project outline, the development of the concept for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a SGB V was supported by 3 modules:

- Empirical information from the benefit assessments of drugs according to the Act on the Reform of the Market for Medicinal Products (AMNOG, §35a SGB V).
- Exploratory literature search for scientific questions arising as part of the conceptual work (e.g. on the informative value of studies without randomization, depending on existing data constellations).
- Interviews with registry experts on criteria for the quality and methodological requirements of the data collected within the framework of the respective generation of data.

Determination of quality criteria for patient registries

During the course of the project, it became apparent that, for the generation of routine practice data for the benefit assessment of drugs, besides specifically conducting studies to generate data (study-specific data collection), data collection from registries is the second relevant data collection tool. The specification of quality criteria for the data collected was therefore limited to registries. The basis for the description of quality criteria was formed by the above-mentioned interviews with registry experts as well as a compilation of quality criteria for patient registries from national and international recommendations.

Results

Routine practice data for the benefit assessment of drugs are defined as follows:

- routine practice data are collected from the patient populations for which there is a therapeutic indication for the drug of interest within the scope of its marketing authorization
- in the collection of routine practice data, patients are treated without specific requirements

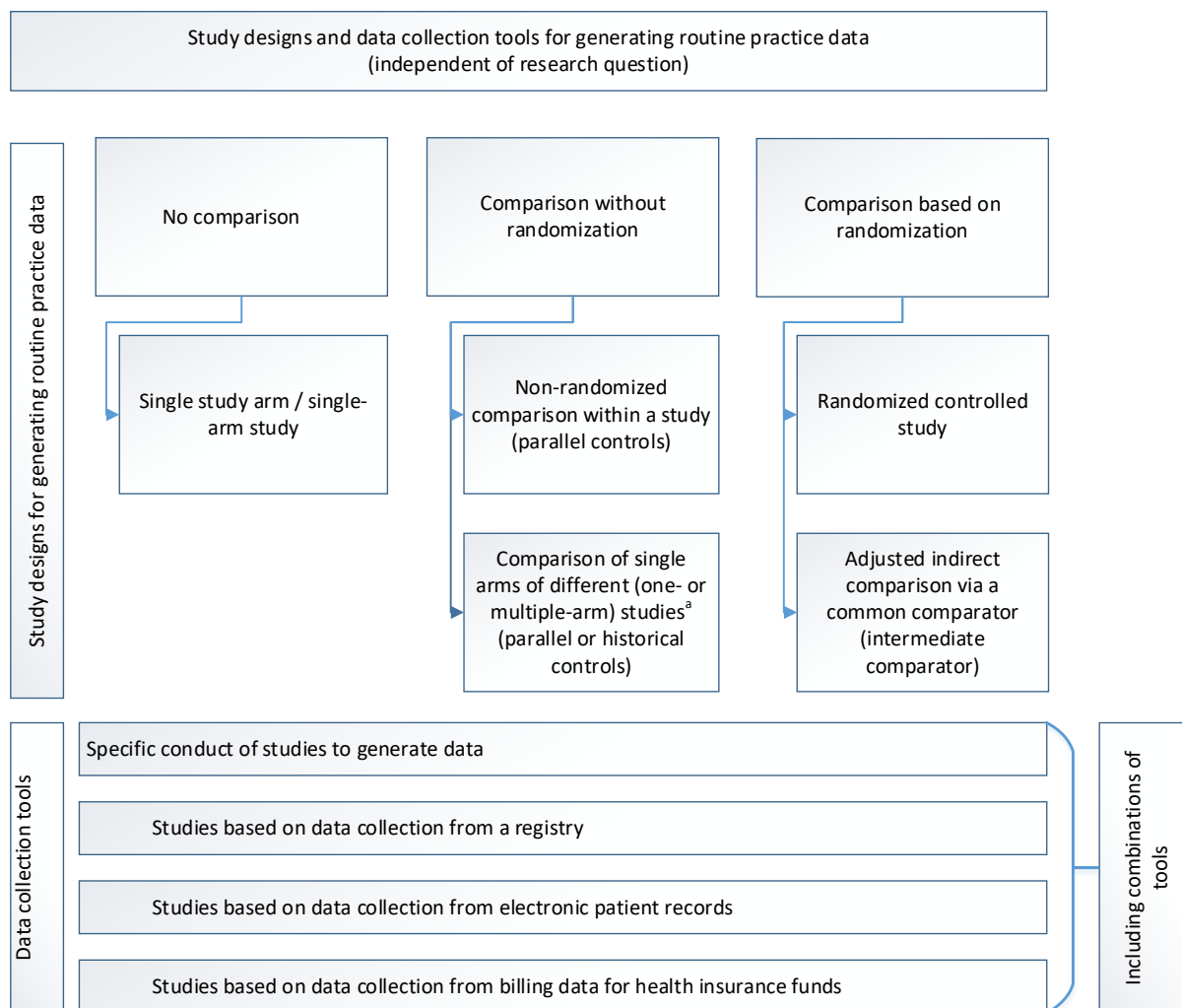
Since drug assessment according to SGB V is concerned with patient care in Germany, routine practice data must meet the two criteria mentioned above so that conclusions can be drawn for health care in Germany.

The definition of routine practice data implies neither a specific study design nor a specific data collection tool.

The goal of collecting routine practice data does not require that data collection be limited to data collected in routine practice per se. Rather, such a misconceived restriction of data collection would jeopardize the goal of the benefit assessment. The benefit assessment regularly requires data that are not collected in routine practice for all patients (e.g. data on health-related quality of life, symptoms or side effects). For use in a benefit assessment, routine practice data must also be sufficiently valid and structured.

Overview of study designs and data collection tools with the aim of generating routine practice data

The following figure provides an overview of study designs and data collection tools that can be used to generate routine practice data. The upper part of the figure describes the study designs that are basically conceivable, depending on the possible type of comparison of interventions. The lower part names the tools that can be used to collect routine practice data in studies with different designs. It becomes clear that the various data collection tools can generally be used for all study designs.



a: including studies on the spontaneous course of the disease

Figure 1: Study designs and data collection tools for generating routine practice data

Routine practice data in benefit assessments

If routine practice data are to be used for a benefit assessment, it must be taken into account that the basis of any conclusion on the effects of interventions is a comparison. This is because only on the basis of a comparison is it possible to distinguish between “**after** intervention A” and “**due** to intervention A”; this distinction is necessary for a causal conclusion.

It follows from these deliberations that the sole consideration of single-arm studies or individual study arms is not relevant for the benefit assessment. Thus, the left-hand strand of the overview of study designs in Figure 1, showing designs without a comparison, is not discussed further. Only comparative study designs are relevant to the research question of the benefit assessment.

Depending on the comparative study design chosen for the generation of routine practice data for a benefit assessment, different requirements for the conduct and analysis of the study arise. Table 1 shows the steps from the definition of the research question of the benefit assessment

to the result of the investigation of this question and summarizes the existing requirements in this process.

While general scientific principles, such as the formulation of the research question to be answered or the interpretation of the results (taking into account the achieved certainty of the results), are performed independently of the study design chosen, other steps of the benefit assessment differ depending on the study design. This is because, for certain study designs a fair, causally interpretable comparison can be assumed while for other designs, this fair comparison needs to be approximated by specific steps in study planning, data collection and analysis.

Table 1: Overview of general and specific requirements for the individual steps in the generation of routine practice data for benefit assessments, depending on study type

Process step	General requirements (for all study types)	Specific requirements for comparative studies without randomization	Specific requirements for comparative studies with randomization	Specific requirements for adjusted indirect comparisons via a common comparator (intermediate comparator)
Formulation of the research question and decision on a study design	<ul style="list-style-type: none"> ▪ Identification of the evidence gap ▪ Formulation of the research question (PICO) according to the evidence gap ▪ Consideration of the requirements for the benefit assessment from §35a SGB V 	<ul style="list-style-type: none"> ▪ No factors that make it unlikely that sufficiently valid results can be achieved with this study design 	<ul style="list-style-type: none"> ▪ No very large (dramatic) effects to be expected for decision-guiding outcomes; outcomes of interest also achievable under comparator therapy 	<ul style="list-style-type: none"> ▪ Availability in principle of studies for such a comparison (preliminary search)
Study planning	<ul style="list-style-type: none"> ▪ Detailed study protocol finalized before the start of data collection ▪ Prespecified analysis plan 	<ul style="list-style-type: none"> ▪ Emulation of the planning of comparative studies with randomization (the target trial) ▪ Prespecification of possible confounders and their adjustment in the analysis 	<ul style="list-style-type: none"> ▪ Adaptation of the study design to the daily treatment routine (pragmatic randomized study: inclusion and exclusion criteria, interventions, outcomes, visits to the doctor) 	<ul style="list-style-type: none"> ▪ Consideration of pragmatic randomized studies in the inclusion criteria ▪ Planning of a systematic review, including definition of the requirements for indirect comparisons
Data collection	<ul style="list-style-type: none"> ▪ The data collection tool chosen must be able to provide data of the required quality 	<ul style="list-style-type: none"> ▪ Ensuring the availability of data for confounder control 	<ul style="list-style-type: none"> ▪ Use of existing data structures, e.g. registries 	<ul style="list-style-type: none"> ▪ If necessary, re-analysis of existing studies to meet requirements for indirect comparisons
Analysis und interpretation	<ul style="list-style-type: none"> ▪ Consideration of the informative value of the different study designs and the specific data quality when interpreting the results 	<ul style="list-style-type: none"> ▪ Approximation to the similarity of the groups in terms of prognostic factors through adjustment 	<ul style="list-style-type: none"> ▪ Analysis and interpretation following existing standards 	<ul style="list-style-type: none"> ▪ Examination of the conditions for indirect comparisons (similarity, homogeneity, consistency of studies)
PICO: patient, intervention, comparison, outcome; SGB: Sozialgesetzbuch V (Social Code Book V)				

Choice of design and study planning

The decision on a study design should take into account whether sufficiently valid results for a benefit assessment can be achieved with the design chosen.

An adequate study design that is also comprehensible in its timing is of decisive importance for the validity of the results of a study. A study protocol and a statistical analysis plan should be prepared before the study starts, and the study should be registered in a study registry.

For the planning of comparative studies without randomization, in order to compare treatment effects, the explicit replication of the planning of comparative studies with randomization is recommended (emulation of target trials).

Adjustments to compensate for the influence of structural inequality of treatment groups are essential for the data analysis of studies without randomization. In order to avoid a results-driven analysis, the relevant confounders and the procedure of the adjustment in the analysis must be prespecified comprehensibly and in the necessary depth of detail in the study protocol. The relevant confounders must be systematically identified (e.g. on the basis of scientific literature with the involvement of subject experts) and prespecified in the study protocol. The availability of corresponding data in the selected data source must be ensured before deciding on a comparative study without randomization. Adjustment only for the confounders available in the data set is insufficient if the relevant confounders are not covered.

When conducting a comparative study without randomization, it is possible to collect the data retrospectively or prospectively or in combination (partly retrospectively and partly prospectively). Retrospective data collection only makes sense if the data set on the basis of which the retrospective data collection is to be conducted contains the necessary data in the quality required. The availability of the relevant data must be ensured before deciding on a retrospective design. Historical controls are possible if the patient populations studied in the past are sufficiently similar to the patient population currently being treated and if data of sufficient quality for a meaningful comparison have been collected in the past. In addition, specific data relevant to the current study (e.g. individual patient data on confounders) must be available from the historical data set, and the data must be sufficiently similar (e.g. outcomes and confounders defined and corresponding data collected in a sufficiently similar manner).

If the necessary data are not available in sufficient quantity or quality, prospective data collection is required. If possible, existing data sources can be used (e.g. indication-specific clinical registry) in which any missing data (e.g. individual outcomes) can be added to the data set in the prospective data collection.

Data collection tools

The various data collection tools (study-specific data collection, registries, electronic patient records and claims data of health insurance funds) can in principle be used for comparative studies without randomization as well as for studies with randomization.

In practice, the collection of routine practice data from electronic patient records and claims data of health insurance funds for use in a benefit assessment does not appear realistically feasible at present and in the near future. The main reasons are the limited representation of relevant data for the benefit assessment (patient characteristics and outcomes) and the limited data quality of these sources.

In addition to study-specific data collection, patient registries covering a given disease (disease registries) are particularly suitable for data collection for benefit assessments. This is because, of the data collection tools that are not primarily geared towards comparative studies, such registries are most likely to offer the option of adapting the data collection to the requirements of these studies. This concerns both the specification of the necessary data and the data quality. In recent years, the aims and scope of the documentation implemented in registries have been expanded. In particular, the increasing documentation of clinical information in registries that can be used to describe the PICO (population, intervention, comparison, and outcome) for benefit assessments is relevant in this context. If a registry is expandable in principle, the combination with a supplementary, study-specific data collection for the respective registry study is also conceivable.

Studies based on data collection in a registry

Conceptually, it is important to distinguish between registries (active, prospective, standardized documentation of observation units on predefined questions, but expandable over time) and studies in these registries (registry studies). In principle, non-interventional and interventional comparative studies are possible in registries. In registries, comparative studies without as well as with randomization can be conducted.

Data quality requirements

Several national and international guidelines, overviews and position papers are available to describe data quality requirements in registries. These are broadly consistent in their main features. Ultimately, however, it is neither decisive nor necessary that all the measures mentioned there have been fully implemented, but rather that the data relevant to the specific research question are available in such a quality that an analysis within the framework of a registry study can be reliably interpreted. To ensure this, various categories of quality criteria for the data of a registry can be distinguished (see Table 2).

Table 2: Criteria for data quality and for ensuring the quality of routine practice data collection for the benefit assessment of drugs

Category	Quality criteria
Mandatory criteria to ensure data quality	<ul style="list-style-type: none"> ▪ Detailed registry description (aim, registry protocol) ▪ Exact definition / operationalization of exposures, clinical events, outcomes and confounders ▪ Current data plan / coding manual ▪ Training on data collection and recording ▪ Clearly defined inclusion and exclusion criteria for registry patients ▪ SOP system for data collection ▪ Package of measures to ensure the accuracy of data and to provide information on error rates (e.g. source data verification, internal and external audits, IT-supported checks [e.g. cross-reference checks]) ▪ Documentation trail - documentation of process and definition changes in the registry ▪ Scientific independence of the registry ▪ Sustainable financing
General criteria that are regularly relevant for registry studies for benefit assessments	<ul style="list-style-type: none"> ▪ Use of exact dates for patients, disease and events ▪ Detailed information on the drug therapy (active substance, dose, dose change, including dates) ▪ Timeliness (including rapid availability and punctuality of the required results)
General criteria that may be relevant for registry studies for benefit assessments, depending on the research question	<ul style="list-style-type: none"> ▪ Use of standard classifications (e.g. ICD-10) and terminology (e.g. MedDRA) ▪ Use of valid standard survey tools (questionnaires, scales, tests) ▪ Flexibility and adaptability (e.g. for embedding studies, for further data collection, in the event of changes in the health care situation) ▪ Linkability with other data sources
Criteria whose degree of fulfilment is to be assessed with regard to components of the research questions ^a	<ul style="list-style-type: none"> ▪ Representativeness of the sample / selection of the sample ▪ Completeness of data per data collection time point (lost-to-follow-up, drop-outs) ▪ Completeness of data collection time points ▪ Correctness of data ▪ Collection of data on all confounders relevant for the research question ▪ Data consistency over time
<p>a: The criteria mentioned are important criteria of data quality, but can only be assessed in relation to specific questions. On the one hand, for example, “accuracy of data” and “consistency of data over time” only refer to data that are relevant to the respective question. On the other hand, “representativeness of the sample” refers only to the population relevant to the research question, but not to the entire registry population.</p> <p>ICD: International Statistical Classification of Diseases and Related Health Problems; IT: information technology; MedDRA: Medical Dictionary for Drug Regulatory Affairs Activities; SOP: standard operating procedure</p>	

In the context of the suitability testing of a specific registry, this list of criteria should be used to assess for each specific research question

- whether and to what extent the individual criteria are fulfilled
- what influence a possible non-fulfilment is likely to have on the quality of the results, and

- whether possible deficits can be corrected in a registry-based study using a reasonable amount of resources.

Interviews with registry operators

From the interviews with the registry operators, it emerged that the suitability of the respective registry for the benefit assessment of drugs cannot be answered in a generalized manner, but depends on the specific research question. However, from a technical and organisational point of view, the registries are usually prepared to implement any necessary extensions of the data set.

It was also possible to deduce various factors from the interviews that are beneficial or obstructive to the operation of the registry. From this and generally from the results of the interviews, recommendations for action can be derived for registry operators, those responsible for registry studies, as well as health care and health policy decision-makers.

Requirements for the analysis

In studies without randomization, the groups to be compared cannot be considered similar in terms of prognostic factors. This similarity that is required for a fair comparison is generally not given in these studies. Group differences concerning possible confounders, i.e. factors that are related to both treatment and outcomes and can consequently distort a treatment effect, must therefore be considered when estimating effects. A detailed study protocol and analysis plan should thus describe, among other things, the systematic identification of relevant confounders (e.g. by means of the scientific literature with the involvement of experts), since confounder adjustment must be based on which confounders are relevant to the research question and not on which ones are included in the data set.

Various approaches are available for confounder adjustment: for a benefit assessment of drugs, as a rule only those approaches using individual patient data are meaningful. The use of propensity scores is a frequently applied method for the consideration of confounders in comparative studies without randomization based on registries. When using the propensity score method, important criteria include positivity, overlap and balance. The relevant decision structure must be defined in the analysis plan; this structure should also contain specifications for decisions depending on the specific data situation (e.g. minimum level of overlap and balance).

In practice, even if the usual methodological guidelines are strictly followed, the accuracy of the assumptions regarding confounder adjustment cannot be fully verified and unmeasured or completely unknown confounders may play a role. Therefore, results from comparative studies without randomization as a rule at best provide only a low degree of qualitative certainty of results. Even if studies without randomization only show a low qualitative certainty of results, they can increase the certainty of results of the overall conclusion on added benefit if combined with other data (e.g. if reliable data on important outcomes are supplemented by the study

without randomization in other outcome categories, or if a [small] study with randomization is combined with a [larger] study without randomization).

Even with the most careful analysis and fulfilment of the quality requirements mentioned above, due to potentially unknown confounders, a conclusion on the benefit or harm of an intervention should only be derived from the effects observed in the study if these effects exceed a certain effect size. A (positive or negative) conclusion on the benefit or harm can be drawn if the confidence interval for the effect observed exceeds a threshold that must be defined. Since the fulfilment of the above-mentioned quality requirements is a prerequisite for the observation of effects, this threshold value should be significantly below the value for the “dramatic effect” (relative risk of 5-10), e.g. in a range of 2-5 for the relative risk. The specific threshold depends on the quality of the data in the individual case.

In benefit assessments of drugs according to §35a of SGB V, starting from this threshold for a conclusion on benefit or harm, if the threshold is exceeded, there is at least a minor added benefit for the respective outcome. Exceptions are outcomes in the category “non-serious/non-serious complications”, because, according to the Regulation for Early Benefit Assessment of New Pharmaceuticals², a “not only marginal improvement” is additionally required for these outcomes. For all outcome categories, classification into the extent categories “considerable” or “major” requires higher (i.e. above the above-mentioned threshold) effect sizes that are graded according to magnitude.

Especially for rare diseases, it may be useful and necessary to conduct studies in international collaboration. On the one hand, such analyses require standardized data harmonization. On the other, analyses that use data generated outside of the German healthcare context of interest must justify that these data can be classified as routine practice data in terms of health care in Germany or that deviations are not relevant for the effect estimate. In the case of analyses from several registries, it can for efficiency reasons be useful not to form a common data pool and then analyse it, but to plan and conduct identically designed studies in the individual registries and then to summarize these studies meta-analytically.

Reporting requirements

Irrespective of the study type, the complete documentation of a study includes the study protocol (planning of the methods and conduct of the study), the analysis plan (planning of the data analysis) and the results report (description of the planned methods [including the analysis] and conduct of the study, deviations from this planning and reporting of complete results). The study protocol and the analysis plan serve not only to describe the methods and conduct of the study in the case of prospectively collected data, but also to prespecify the study planning. This prespecification is an essential quality feature of a study with prospective data collection. For prospective comparative studies without randomization, this prespecification should cover

²Arzneimittel-Nutzenbewertungsverordnung

confounder control (documentation of confounders and definition of adjustment methods) as comprehensively as possible.

The possibility of results-driven analyses and reporting is an unsolved problem for retrospective study designs. Irrespective of this, a study protocol including an analysis plan should also be prepared for studies with retrospective data collection from existing data sets. It is recommended to make these documents publicly available.

Optimized studies for decision-making in health care

The conduct of a high-quality comparative study without randomization is resource-intensive. In this context, the current discussion about adjustments in the conduct of comparative studies with randomization is relevant. On the one hand, this should ensure that the results are meaningful for broader populations (pragmatic studies with randomization) and, on the other hand, reduce the necessary effort (“large simple trials” and registry-based studies with randomization). In summary, it may be easier and more purposeful to conduct a comparative study with randomization considering these adjustments than to try to generate high-quality results from a comparative study without randomization.

Suggestions for an approach to routine practice data collection according to GSAV and §35a (3b) SGB V

In the present rapid report, the results of the project were also analysed in connection with the possibility of routine practice data collection introduced by the “Gesetz für mehr Sicherheit in der Arzneimittelversorgung” (GSAV³, Law for More Safety in the Supply of Medicines [own translation]).

Definition of the research question

The basis for routine practice data collection according to GSAV is the definition of the research question to be answered by this data collection. The question at least contains the components of the PICO format and the required duration of data collection. The exact specifics of the research question are derived from the evidence gap shown in the benefit assessment and that is to be closed by the data collection. A research question defined in this way is also the starting point for the description of the necessary scope of data collection (including duration of observation and sample size calculation).

Evidence gaps in benefit assessments of drugs (orphan drugs)

In order to be able to better assess the evidence gaps in benefit assessments and their importance in determining the extent of added benefit, G-BA decisions on benefit assessments of orphan drugs were examined in more detail. Decisions on orphan drugs with market access in the years

³Gesetz für mehr Sicherheit in der Arzneimittelversorgung

2014 to 2018 were examined, including decisions on new therapeutic indications for orphan drugs in this period.

On the one hand, the analysis shows that, for orphan drug assessments in the years 2014 to 2018, relevant data were submitted for a large part of the research questions in the corresponding dossiers for the benefit assessments at the time of market access (80 of 85 questions, 94%). In about two-thirds of the cases, these were studies with randomization, and in one third of the cases, without randomization. Nevertheless, an added benefit of the intervention was quantified for only about a quarter of all research questions. It could not be inferred from the analysis that the added benefit was particularly non-quantifiable in very small target populations.

The analysis of the research questions with the conclusion of a non-quantifiable added benefit showed that in 61% (52 of 85) of the research questions assessed by the G-BA for the years 2014 to 2018, evidence gaps were identified that were decisive for the lack of quantifiability of added benefit. In consequence, almost two-thirds of the orphan drug assessments are potential candidates for routine practice data collection according to GSAV. In all 52 cases, data on the control group were also missing, which is why targeted routine practice data collection according to GSAV must as a rule be planned and conducted in a comparative manner involving a control group (comparator therapy).

Evidence gaps are often present in several outcome categories (mortality, morbidity, health-related quality of life, and adverse events). With regard to morbidity and health-related quality of life, information on patient-reported outcomes (PROs) will often be required for targeted routine practice data collection according to GSAV, as these are essential for addressing the evidence gaps in these outcome categories.

It is therefore overall foreseeable that a data collection required by a regulatory authority, which is intended in particular to identify rare or late-onset side effects of the respective orphan drug, will in unchanged form often not represent a suitable data collection for a benefit assessment (i.e. a targeted routine practice data collection according to GSAV). Which change or extension to a regulatory data collection is necessary to achieve suitability for a benefit assessment has to be examined in each individual case based on the existing evidence gap for the quantification of the added benefit.

Possible process steps of routine practice data collection according to GSAV

Based on the analysis of the orphan drug assessments from 2014 to 2018 and on the requirements of SGB V, Table 3 shows possible process steps of the routine practice data collection according to GSAV in the benefit assessment procedure according to §35a SGB V.

Table 3: Process steps for routine practice data collection according to GSAV for benefit assessments according to §35a SGB V

Process step	Comment
Identification of an evidence gap in the G-BA decision on a benefit assessment according to §35a SGB V	<ul style="list-style-type: none"> Evidence gap: relevant data gap for the comparison of the new drug with the (appropriate) comparator therapy with regard to patient-relevant outcomes (especially if the evidence gap does not allow quantification of the added benefit)
Description of the G-BA specifications for routine practice data collection according to GSAV and transmission to the pharmaceutical company	<ul style="list-style-type: none"> Definition of the research question Duration, type and scope of data collection (duration of data collection per patient, sample size based on a sample size estimation) Type and scope of the analysis (depending on the study type used) Specification of the time points for the evaluation of the data obtained (at least every 18 months) Specification of the requirements, taking into account ongoing and planned data collection, especially those resulting from requirements of the regulatory authorities (e.g. EMA)
Evaluation of the data collected and the obligation to collect data	<ul style="list-style-type: none"> At the time of the first evaluation, the G-BA will check whether a (publicly available) study protocol including an analysis plan is available that reflects the routine practice data collection according to GSAV as requested At the first and each subsequent evaluation time point, the G-BA will evaluate the available data and decide whether the data collection can be stopped or should be continued
EMA: European Medicines Agency; G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee); GSAV: Gesetz für mehr Sicherheit in der Arzneimittelversorgung (Law for More Safety in the Supply of Medicines [own translation])	

Conclusion

Study design and data collection

- The use of routine practice data for benefit assessments of drugs according to §35a SGB V requires a comparison between the new drug and the appropriate comparator therapy specified by the G-BA; this requires the conduct of comparative studies.
- The collection of routine practice data from electronic patient records and from claims data of health insurance funds for benefit assessments according to §35a SGB V is currently and foreseeably not considered realistic; rather, a study-specific data collection or data collection from patient registries is necessary

Routine practice comparative studies without randomization

- If comparative studies without randomization are to be used for the benefit assessment, it must be ensured at the stage of study planning that the study conduct and the data collected are of the quality required to generate interpretable results.
- Essential components of such a study planning are a study protocol including an analysis plan, the emulation of a target trial that deals with the relevant research question, and ensuring that sufficient data are collected for confounder control.

- A key aspect of the analysis of a comparative study without randomization is adequate confounder adjustment; this adjustment must be pre-specified as far as possible and the assumptions made (e.g. the definition of the relevant confounders) must be substantiated.
- No effects can be derived from comparative studies without randomization if the data quality in the data sources used and the quality of analysis and reporting is not high.
- Even under high quality requirements (for data, analysis and reporting), no more than a hint of an effect can normally be derived from comparative studies without randomization.
- Due to the inherent uncertainty of the results from comparative studies without randomization, because of potentially unknown confounders, a conclusion on the benefit or harm of an intervention should only be derived from the effects observed in the study if these effects exceed a certain effect size. Quantification of an added benefit according to the legally prescribed extent categories requires corresponding effect sizes graded according to magnitude.
- The possibility to consider retrospective study designs depends on whether the available data sources already contain the necessary data in the required quality; comparisons of a new drug with historical controls only appear realistic if the same data source (e.g. a disease-specific clinical registry) is used for the new drug and the historical control.

Routine practice comparative studies with randomization

- Routine practice comparative studies can also be randomized (pragmatic clinical trials).
- The effort required for a routine practice comparative study with randomization will generally – with comparable data quality – be less than the effort required for a study without randomization, as confounder data collection and confounder adjustment can be omitted.
- Routine practice comparative studies with randomization are of higher informative value than those without randomization, and the quantification of added benefit is more reliable.
- Especially after market authorization, depending on the existing research question, routine practice comparative studies with randomization can be conducted with limited data collection ([large] simple trials); conducting them in registries has an additional potential to accelerate the conduct of the studies and make them less complex and resource-intensive (registry-based comparative studies with randomization).

Routine practice data collection according to GSAV

- Whether the various patient registries are currently already suitable for data collection according to §35a SGB V cannot be answered in general, as this depends on the respective registry and the specific research questions posed.
- On the basis of the analyses and the discussions with the registry operators, fields of action can be described that serve to support the individual registries in particular and the

registry landscape in Germany in general in routine practice data collection according to GSAV; these fields of action are described in the report.

- The findings of the present report can be used for routine practice data collections according to GSAV to close evidence gaps after a benefit assessment; a proposal for the corresponding approach is provided with the report.

The full report (German version) is published on

<https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-43-scientific-elaboration-of-concepts-for-the-generation-of-data-related-to-clinical-practice-and-their-evaluation-for-the-purpose-of-benefit-assessments-of-drugs-35a-social-code-book-v-rapid-report.11901.html>