Journal of
Market Access & Health Policy

MDPI

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Target Population Estimation in German Orphan Drug HTA: Trends and Differences in Epidemiological Data Sources

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Abstract

Estimating target populations for orphan drugs is challenging because epidemiological evidence is limited and heterogeneous. We examined data sources used in German health technology assessment (HTA), temporal trends, and differences between oncology and non-oncology procedures. We retrospectively analyzed German orphan drug HTA procedures completed from 2012 to 2025. Public manufacturer dossiers, IQWiG assessments, and Federal Joint Committee resolutions were reviewed, and procedures classified by the primary epidemiological source were used to derive the final statutory health insurance target population estimate. Among 162 procedures, Literature was the most frequent primary source (43.2%), followed by Literature and Registry data (17.3%), Routine data (16.0%), and Registry data (15.4%). Use of Routine data increased from 3.7% in 2012–2015 to 25.0% in 2021–2025. Source distributions differed significantly between oncology and non-oncology procedures ($\chi^2(3) = 36.8$, $p < 0.001$; Cramér's V = 0.477), with greater use of registry-based sources in oncology. An exact Monte Carlo analysis of the unpooled table confirmed the association ($p < 0.0001$). Epidemiological evidence sources were heterogeneous, while use of Routine data increased substantially over time. Stronger registries, coding systems, and responsible secondary use of healthcare data may improve future rare disease target population estimates.

Keywords: orphan drugs; health technology assessment; rare diseases; epidemiology; target population; Germany

1. Introduction

Health technology assessment (HTA) plays a central role in evaluating the clinical and economic value of newly introduced pharmaceutical products and informs pricing, reimbursement, and access decisions in many healthcare systems [1]. A key component of these assessments is the estimation of the relevant target population, as the expected number of eligible patients directly affects healthcare planning and the interpretation of treatment value [2].

Rare diseases, defined in the European Union as conditions affecting fewer than 5 in 10,000 individuals, present significant challenges in healthcare evaluation, particularly in the estimation of affected patient populations [3]. Accurate epidemiological data, including prevalence and incidence, are crucial for determining the size of the target population that may benefit from new medical interventions. This issue is particularly relevant for orphan drugs, which by definition address diseases characterized by small patient populations.

In practice, many rare diseases are underdiagnosed, variably classified, or insufficiently captured in routine healthcare documentation. Disease definitions may evolve over time,

Check for updates

Academic Editor: Borislav Borissov

Received: 5 October 2026
Revised: 4 November 2026
Accepted: 10 November 2026
Published: 16 November 2026

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coding systems may lack specificity, and clinical expertise is often concentrated in specialized centers. Consequently, robust estimates of prevalence and incidence are difficult to obtain, particularly when no specific ICD-10 code exists, and broader proxy codes may increase misclassification or underreporting and limit the comparability and epidemiological usefulness of administrative healthcare data [4,5].

As a result, manufacturers often draw on heterogeneous evidence sources, including literature, registries, routine healthcare data, expert assumptions, modeling approaches, extrapolations, or combinations of several sources. Each source type has potential advantages and limitations: literature may provide disease-specific depth but can be outdated or heterogeneous; registries may offer clinically validated information but remain incomplete; and routine data may provide broad coverage but depend on coding quality and diagnostic validity.

Germany represents a relevant setting for studying epidemiological evidence generation in HTA because it combines a large healthcare market with an established national benefit assessment process. Under the Arzneimittelmarktneuordnungsgesetz (AMNOG), newly authorized medicinal products undergo an early benefit assessment pursuant to §35a SGB V [6]. Pharmaceutical companies are required to submit detailed dossiers to the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), including evidence relevant to the expected target population and eligible patient subgroups [7].

For orphan drugs, a dedicated pathway applies in which added benefit is deemed proven by regulatory approval up to a defined annual revenue threshold [6]. Nevertheless, the size of the relevant target population remains a key parameter within the overall assessment framework and subsequent reimbursement discussions and is highly relevant for evaluating the clinical and economic impact of a new intervention.

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG), which is tasked with assessing these dossiers, critically appraises the manufacturer's derivation of target population estimates and treatment costs as part of orphan drug benefit assessments. In practice, these evaluations focus on the transparency, validity, reproducibility, and underlying assumptions of the submitted analyses and may identify inconsistencies, uncertainties, or limitations in the supporting evidence base [2,7]. Despite the practical relevance of epidemiological evidence in this context, little is known about which data sources are used in German orphan drug HTA procedures, how these patterns have evolved over time, and whether meaningful differences exist across therapeutic areas. To our knowledge, systematic cross-procedure analyses of epidemiological evidence generation in German orphan drug HTA remain scarce.

This study systematically assessed epidemiological data sources used in German orphan drug HTA procedures between 2012 and 2025, including temporal trends and differences between oncology and non-oncology indications. The analysis aims to improve understanding of current evidence-generation practices for target population estimation in rare disease HTA.

2. Materials and Methods

2.1. Study Design

A retrospective cross-sectional study was conducted to evaluate the epidemiological data sources used for target population estimation in German orphan drug health technology assessment (HTA) procedures.

The study examined completed orphan drug procedures published between 1 January 2012 and 31 December 2025. Starting in 2012 reflects the completion of the first orphan drug benefit assessment under the German AMNOG framework.

The primary objective was to characterize which epidemiological evidence sources were used in practice for deriving target population estimates. Secondary objectives were to assess temporal trends in source use over time and to compare patterns between oncology and non-oncology therapeutic areas.

The unit of analysis was the individual orphan drug HTA procedure after the application of defined selection, curation, and de-duplication rules. The analytical framework, including classification categories and comparison groups, was defined prior to the final statistical analysis.

2.2. Data Sources and Procedure Identification

Eligible procedures were identified through official public listings of completed orphan drug procedures on the G-BA website [8].

Publicly available documents were then systematically reviewed to extract methodological information.

Primary sources included:

- Manufacturer dossiers;
- IQWiG assessments;
- Final G-BA resolutions.

2.3. Inclusion and Exclusion Criteria

Included were all completed German orphan drug HTA procedures formally conducted under the national orphan drug assessment pathway during the study period.

Inclusion criteria:

Procedures were eligible if they met all of the following criteria:

- Formal completion between 1 January 2012 and 31 December 2025;
- Classification as an orphan drug procedure within the German HTA framework;
- Sufficient public information for reliable procedural identification.

During data collection, one otherwise eligible procedure was identified for which no manufacturer dossier had been submitted or was publicly available. Because this represented a relevant procedural characteristic, the case was retained in the analytical dataset and categorized separately as not available (no dossier).

Exclusion criteria:

The following were excluded:

- Non-orphan drug procedures;
- Procedures completed outside the predefined study period;
- Duplicate procedural records without independent analytical relevance after curation.

2.4. Handling of Repeated Procedures and Duplicate Counting

Because multiple HTA procedures may occur for the same active substance over time, defined rules were applied to avoid duplicate counting and overrepresentation of individual products.

Repeated assessments of the same active substance for an already evaluated therapeutic indication were excluded, regardless of the reason for reassessment. Additional assessments of the same active substance were included only if they concerned a distinct therapeutic indication. Extensions of previously assessed therapeutic indications were not considered independent observations.

Parallel or joint procedures with identical methodological content were excluded where no independent target population derivation was presented.

Repeated procedures were also excluded when the target population estimation fully reused a previous derivation without independently generating a new estimate.

Where classification required judgment, decisions were made according to consistent application of the same rules across the full dataset.

2.5. Data Extraction

For each included procedure, relevant variables were manually extracted using a structured extraction framework.

Extracted variables included:

- Date of procedural completion;
- Active substance;
- Therapeutic area including oncology versus non-oncology classification;
- Epidemiological data source used for target population estimation.

If multiple documents were available, data extraction primarily relied on the corresponding IQWiG assessment, as these reports typically provided the most structured summary of epidemiological derivation methods. Manufacturer dossiers were consulted when additional detail or clarification of the calculation pathway was required. Data extraction and source classification were performed independently by two authors. Discrepancies were resolved through discussion and, if needed, by consensus. Where information was unavailable, variables were coded as missing or not available.

2.6. Classification of Epidemiological Data Sources

Each procedure was assigned to one category based on the primary epidemiological data source reported as being principally used for derivation of the final GKV target population estimate in publicly available assessment documents, primarily IQWiG reports. Combination categories were assigned when two source types were reported as jointly essential and of comparable relevance for the final estimate. Where one source clearly predominated and the second served only a supportive role, the dominant source category was assigned.

The predefined categories were:

- Literature;
- Registry data;
- Routine data;
- Literature and Registry data;
- Literature and Routine data;
- Registry data and Routine data;
- Not available (no dossier).

Literature:

This category included published epidemiological studies, systematic reviews, meta-analyses, scientific reports, and other publicly accessible external evidence sources.

Registry Data:

This category included disease-specific registries, national or regional patient registries, cancer registries, clinical registries, and dedicated rare disease registries.

Routine Data:

This category included insurance claims data, reimbursement databases, prescription databases, hospital billing datasets, and other routinely collected administrative healthcare data.

Combination Categories:

Combination categories were assigned when two source types were jointly essential for the final target population derivation.

If one source clearly represented the primary basis of estimation and another source served only a supportive, validation, or sensitivity-analysis function, the dominant source category was assigned.

Ambiguous mixed-source cases were resolved by applying these hierarchy rules consistently across the dataset.

Not Available (no dossier):

This category was used for the single eligible procedure for which no manufacturer dossier was available, precluding assignment to an empirical source category.

2.7. Therapeutic Area Grouping

For subgroup analyses, procedures were categorized as oncology or non-oncology according to the therapeutic-area classification used in the G-BA procedure records.

This grouping was chosen because oncology often differs structurally from other rare disease areas with regard to registry infrastructure, coding practices, treatment pathways, and epidemiological data availability.

2.8. Statistical Analysis

Categorical variables were summarized using absolute frequencies (n) and percentages (%). The overall distribution of epidemiological data source categories was described for the complete analytical sample. Temporal trends were assessed descriptively across three predefined calendar periods (2012–2015, 2016–2020, and 2021–2025), with relative frequencies calculated for each source category within each period.

Comparisons between oncology and non-oncology procedures were primarily performed using the chi-square test of independence based on pooled contingency tables to ensure adequate expected cell counts and facilitate interpretable effect size estimation. Effect size was quantified using Cramér's V.

As an additional exact analysis, Fisher's exact test for r × c tables with Monte Carlo simulation (100,000 replicates) was performed using the full unpooled contingency table.

Data management and descriptive analyses were conducted using Microsoft Excel. Exact inferential analyses were conducted in R (4.5.3) (R Foundation for Statistical Computing, Vienna, Austria) using the base stats package. A two-sided p-value of <0.05 was considered statistically significant.

2.9. Ethics and Transparency

All analyses were based exclusively on publicly available documents. No patient-level data, confidential company data, or non-public procedural materials were accessed. Therefore, ethics committee approval was not required.

Classification rules were iteratively refined during dataset curation to ensure consistent treatment of repeated procedures, mixed-source derivations, and edge cases across the full study sample.

All methodological decisions were documented within the study database to maximize transparency and reproducibility of the final analytical dataset.

3. Results

A total of 162 completed orphan drug HTA procedures were included in the final analytical sample.

3.1. Overall Distribution of Epidemiological Data Sources

The distribution of primary epidemiological data sources used for derivation of target population estimates across included German orphan drug HTA procedures is presented in Figure 1.

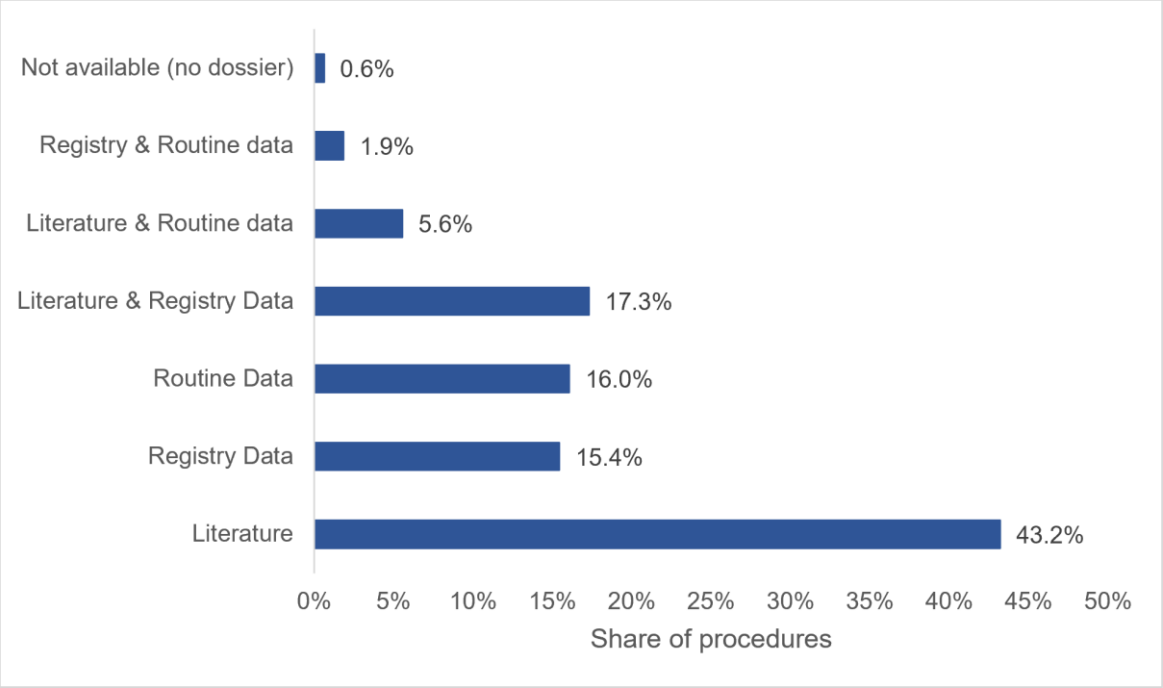


Figure 1. Primary epidemiological data sources (%).

Literature was the most frequently used primary epidemiological data source (43.2%, $n = 70$). Combination approaches using Literature and Registry data accounted for 17.3% ($n = 28$), followed by Routine data (16.0%, $n = 26$) and Registry data (15.4%, $n = 25$).

Less frequently used categories included Literature and Routine data (5.6%, $n = 9$) and Registry and Routine data (1.9%, $n = 3$). Only one procedure (0.6%) could not be classified because no manufacturer dossier was publicly available.

Overall, combination-source approaches represented 24.7% of all included procedures, while single-source approaches based on the Literature, Registry data, or Routine data together accounted for nearly three quarters of the analytical sample.

The findings indicate that although literature-based estimates remained the dominant approach, a substantial proportion of procedures relied on multi-source derivation strategies.

3.2. Temporal Trends in Epidemiological Data Source Use

Temporal changes in epidemiological data source use were observed across the study period (Figure 2).

Literature remained the most frequently used category throughout all three predefined time intervals, accounting for 40.7% of procedures in 2012–2015, 47.5% in 2016–2020, and 40.8% in 2021–2025.

The largest temporal shift was observed for Routine data, which increased from 3.7% in 2012–2015 to 10.2% in 2016–2020 and 25.0% in 2021–2025.

Registry data declined modestly over time (18.5%, 15.3%, and 14.5%, respectively). Combination-source categories generally decreased across the study period, particularly Literature and Routine data, which fell from 11.1% to 1.3%.

The relative stability of literature-based approaches, together with the marked increase in Routine data, suggests a gradual broadening of the evidence base used for target population estimation over time.

Overall, the temporal pattern indicates increasing reliance on routinely collected healthcare data, while registry-based approaches remained comparatively stable or declined slightly.

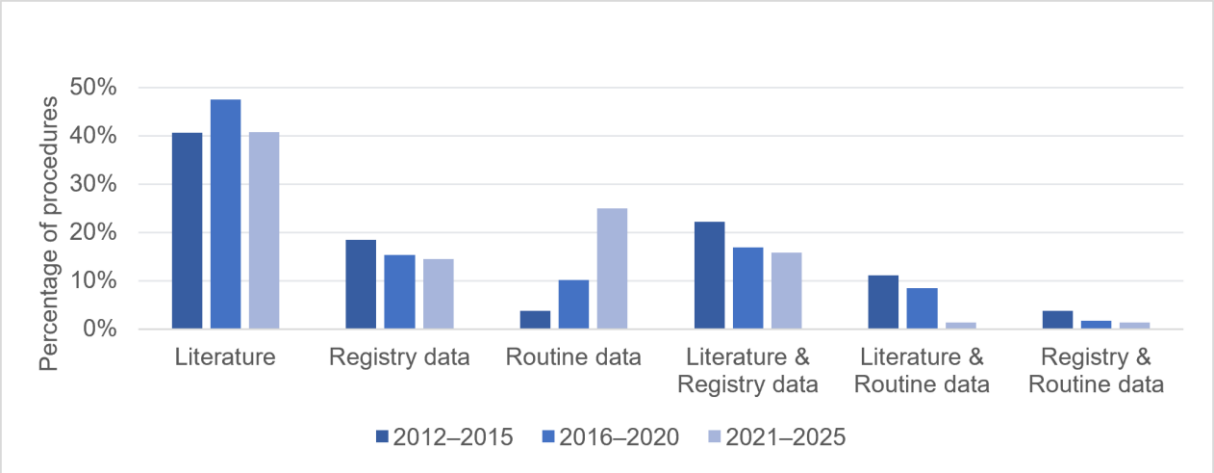


Figure 2. Temporal trends in epidemiological data sources (2012–2025).

3.3. Comparison Between Oncology and Non-Oncology Procedures

Marked differences in epidemiological data source use were observed between oncology and non-oncology procedures (Figure 3).

Among oncology procedures, the most frequently used category was Literature and Registry data (39.3%), followed by Registry data (27.9%) and Literature (24.6%). Use of Routine data was comparatively uncommon (4.9%).

In contrast, non-oncology procedures relied predominantly on Literature (54.5%) and Routine data (22.8%), whereas Literature and Registry data was used in only 4.0% of procedures. Registry data alone accounted for 7.9% of non-oncology procedures.

Less frequent categories, including Literature and Routine data and Registry and Routine data, were observed in both groups at low proportions.

For inferential testing, low-frequency and combination categories were pooled to ensure adequate expected cell counts for chi-square testing. The resulting distribution of source categories differed significantly between oncology and non-oncology procedures ($\chi^2(3) = 36.8$, $p < 0.001$), with a moderate-to-large effect size (Cramér's V = 0.477).

An additional exact Monte Carlo test using the full unpooled 7 × 2 contingency table confirmed the association between therapeutic area and epidemiological data source distribution ($p < 0.0001$).

Overall, oncology procedures showed greater use of registry-based and combination-source approaches, whereas non-oncology procedures more frequently relied on Literature-only and Routine data approaches. The unpooled analysis additionally preserved category-specific heterogeneity, particularly the markedly higher use of Literature and Registry data in oncology procedures (39.3% vs. 4.0%) and the greater use of Routine data in non-oncology procedures (22.8% vs. 4.9%).

These findings indicate distinct evidence-generation patterns across therapeutic areas, with oncology appearing to draw more frequently on structured registry-based evidence and non-oncology procedures more commonly relying on the Literature and administrative Routine data.

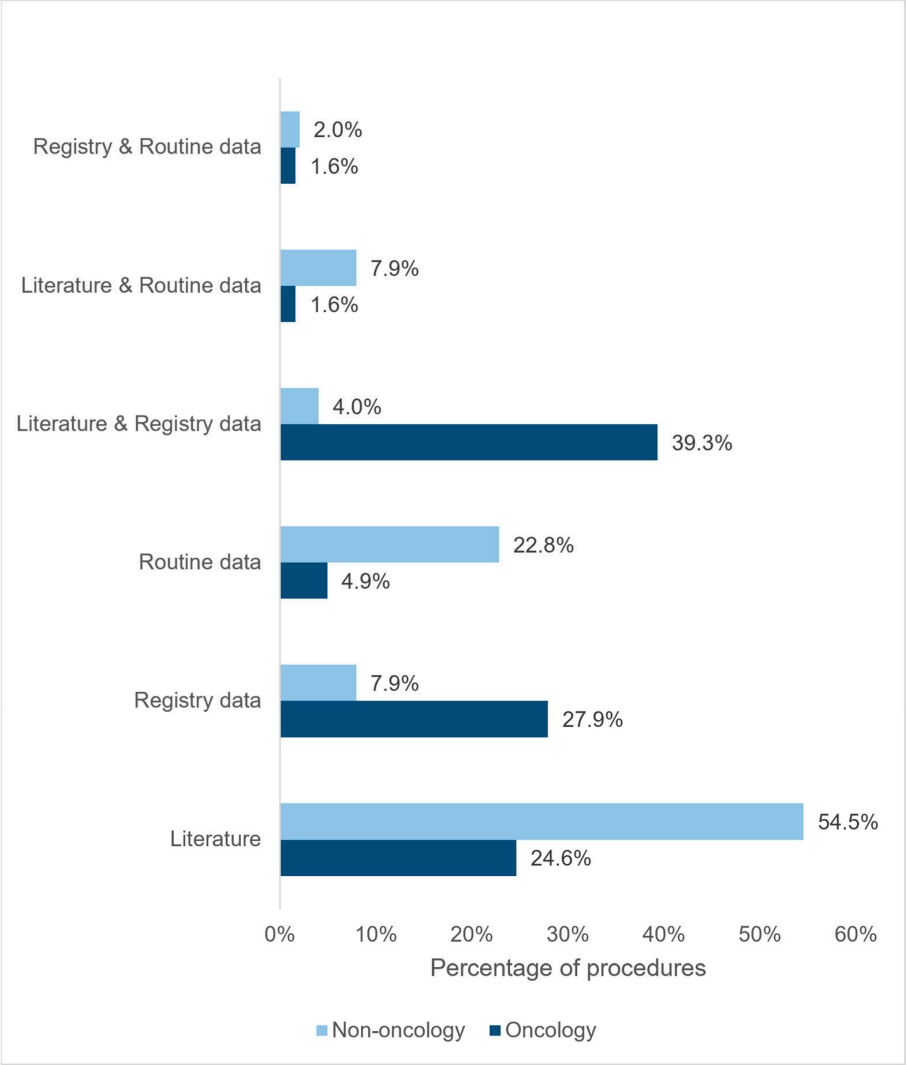


Figure 3. Oncology vs. non-oncology by epidemiological data source.

4. Discussion

This study provides a systematic overview of the epidemiological data sources used to estimate target populations in German orphan drug HTA procedures over more than a decade. Three findings stand out: literature-based approaches remained dominant, the use of Routine data increased substantially over time, and source distributions differed markedly between oncology and non-oncology procedures.

Literature was the primary source in 43.2% (70/162) of procedures, while a further 17.3% (28/162) combined Literature and Registry data. For many rare diseases, published studies may remain the most accessible source of prevalence or incidence estimates because dedicated registries are incomplete or unavailable and routine datasets may lack sufficiently specific codes. Literature-based estimates nevertheless require careful interpretation because case definitions, populations, observation periods, and geographical settings may differ, and the evidence may be outdated or selectively reported. Literature is therefore not inherently inferior but often represents a pragmatic response to limited epidemiological infrastructure. Its credibility depends on transparent source selection, justified assumptions, and transferability [4,5,9].

A second major finding was the clear increase in the use of Routine data, from 3.7% in 2012–2015 to 10.2% in 2016–2020 and 25.0% in 2021–2025. This development may reflect improved data access, greater analytical experience, and increasing expectations for trans-

parent and reproducible estimation. Claims, reimbursement, hospital, and prescription data can provide broad population coverage, longitudinal observation, and analyses that can be updated over time. However, Routine data are not inherently superior to other sources. Their usefulness depends on coding quality, diagnostic specificity, completeness of capture, healthcare utilization patterns, and validated case-identification algorithms. Proxy codes may result in misclassification or under-ascertainment when no disease-specific code is available [4,5,10].

Source patterns also differed by therapeutic area. Oncology procedures more frequently used Literature and Registry data (39.3%) or Registry data alone (27.9%), whereas non-oncology procedures relied predominantly on Literature (54.5%) and Routine data (22.8%). One possible explanation is the comparatively mature oncology data ecosystem, including established cancer registries and structured documentation. Nevertheless, registry utility depends on population coverage, complete and timely case capture, diagnostic verification, standardization, and sustainability. Center-based or voluntary registries may be selective and insufficiently representative [11,12]. In many non-oncological rare diseases, patients remain dispersed across specialties and care settings, diagnosis may be delayed, and systematic capture is less established.

Confidence in a target population estimate cannot be inferred from the nominal source category alone. This study did not assess the accuracy or methodological quality of individual estimates. Literature-based estimates may be credible when assumptions and derivation steps are transparent. Conversely, Registry or Routine data analyses may remain uncertain when coding algorithms, denominators, extrapolations, or assumptions are insufficiently documented. Given the constraints of rare disease epidemiology, residual uncertainty is often unavoidable. Transparent reporting and scenario or range-based analyses may therefore be more informative than single-point estimates that imply unwarranted precision.

Current German initiatives, including the draft of a Medical Registries Act (March 2026) and the Research Data Centre for Health (opened October 2025), may broaden the availability and use of Registry and Routine data [13,14]. Whether these developments improve target population estimation will depend on data quality, access conditions, valid case definitions, transparent governance, and reproducible methods. Future research should examine the methodological quality, reproducibility, and decision impact of individual target population estimates, including whether specific source types are associated with recurring patterns of criticism or acceptance in HTA. Such research could also compare epidemiological estimates derived from different data sources by assessing differences in population coverage, case definitions, data completeness, and potential sources of bias. Repeated longitudinal analyses could also assess whether emerging Registry and Routine data infrastructures translate into decision-relevant epidemiological evidence for orphan drugs, particularly given persistent challenges related to small numbers and coding validity. Such analyses could additionally examine how the epidemiological data sources used in successive benefit assessments of the same active substance for the same therapeutic indication evolve over time.

Strengths of this study include its national scope, the structured classification of 162 HTA procedures over more than a decade, and the assessment of temporal and therapeutic-area differences. Several limitations should be considered. Classification of mixed-source procedures required judgment despite predefined rules, and assigning complex derivations to one predefined category simplified methodological detail. The analysis was based on publicly available documents and therefore reflects the evidence reported in assessment materials. Temporal comparisons were descriptive and did not account for changes in the composition of procedures over time. The broad non-oncology category also

comprises heterogeneous diseases. Finally, the findings are specific to the German orphan drug HTA framework and may not be directly generalizable to other settings.

5. Conclusions

Epidemiological evidence used in German orphan drug HTA procedures remains highly heterogeneous and strongly influenced by underlying data infrastructure. While literature-based approaches continue to dominate, the increasing use of routine healthcare data suggests a gradual shift toward more scalable and reproducible population estimation strategies.

From a methodological perspective, confidence in target population estimates is unlikely to depend on source category alone; it also depends on the transparency, validity, and reproducibility of the underlying estimation approach. Strengthening disease registries, improving coding systems, enabling responsible secondary use of healthcare data, and promoting clearer methodological standards may therefore be key priorities for future rare disease evidence generation. Future work is needed to assess whether emerging Registry and Routine data infrastructures translate into decision-relevant epidemiological evidence for orphan drugs, given persistent challenges related to small numbers and coding validity.

Author Contributions: Conceptualization, M.R. and B.G.; Methodology, M.R. and B.G.; Validation, M.R. and B.G.; Formal Analysis, M.R. and B.G.; Investigation, M.R. and B.G.; Data Curation, M.R. and B.G.; Visualization, M.R.; Writing—Original Draft Preparation, M.R.; Writing—Review and Editing, M.R. and B.G.; Supervision, B.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study used publicly available data from manufacturer dossiers, G-BA resolutions, and IQWiG reports, with no patient-level information. Therefore, ethics committee approval and patient consent were not needed.

Informed Consent Statement: Not applicable.

Data Availability Statement: All underlying source documents analyzed in this study, including orphan drug dossiers and corresponding IQWiG reports, are publicly available on the G-BA website. The dataset generated from these publicly available sources and supporting the conclusions of this study is available from the corresponding author upon reasonable request.

Acknowledgments: During the preparation of this manuscript, the authors used ChatGPT (OpenAI, GPT-5 model family accessed in 2026) solely for language editing, grammar correction, rephrasing, and stylistic refinement. The authors reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: MR is employed by CSL in the pharmaceutical industry. CSL had no role in the study design; data collection, analysis, or interpretation; manuscript preparation; or the decision to submit for publication. BG declares no competing interests.

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