Development of a method to assess the relationship between the volume of services and the quality of treatment outcomes in rare diseases[1]

RAPID REPORT

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Executive summary

On 9 October 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to describe in a scientific report whether, and if so how, a methodological assessment[2] of the relationship between the volume of healthcare services, i.e. interventions, and the quality of treatment outcomes can also be performed for services used to treat rare diseases with correspondingly low case numbers and an insufficient body of evidence. This assessment is necessary for setting minimum volumes.

Research question

The aim of this investigation is to develop a method for assessing the relationship between the volume of services (VoS) and the quality of treatment outcomes for healthcare services used to treat rare diseases with correspondingly low case numbers and an insufficient body of evidence.

Methods

This commission involves developing ways of assessing the relationship between the VoS and the quality of treatment outcomes in rare diseases. This work was supported by exploratory information retrieval with the aim of identifying methodological documents on the following aspects:

- Methodological derivations of minimum volume requirements for rare diseases from other countries, as well as requirements for hospital certification to treat specific rare diseases
- Overarching methodological literature on minimum volumes for rare diseases
- Methodological literature on the transferability of study results to other populations/interventions

The information retrieval for methodological documents for this commission covered previous methodological work at the Institute on the transferability of study results to other populations/interventions and on minimum volumes, an exploratory literature search in MEDLINE, a website search of other HTA agencies and certification bodies, and, based on previously identified methodological documents, the review of reference lists, the use of the ‘Cited Reference’ function in Semantic Scholar and the ‘Similar Articles’ function in PubMed.

[2] in accordance with §136b (1), Sentence 1, No. 2, SGB V

Methodological key points were formulated that must be taken into account with regard to the transferability of results concerning relationships between the VoS and the quality of treatment outcomes between populations and/or interventions.

Results

Exploratory information retrieval identified no documents from other countries on methodological derivations of minimum volume requirements for rare diseases or requirements for hospital certification to treat specific rare diseases. Likewise, no relevant overarching methodological literature on minimum volumes for rare diseases was identified.

The following method was developed to investigate the relationship between the VoS and the quality of treatment outcomes in rare diseases: IQWiG's first step in processing commissions to assess the relationship between the VoS and the quality of treatment outcomes for certain higher-risk interventions is comprehensive information retrieval (including a systematic literature search) to identify suitable studies. Once suitable studies have been identified, the results are examined for reliability. Restrictions may arise here for the following reasons: lack of precision due to small case numbers and inaccuracies in the billing data used or in the coding, which are more relevant in rare diseases due to the small case numbers. If studies with sufficiently reliable results are identified, the further approach is the same as for previous rapid reports on the relationship between the VoS and the quality of treatment outcomes in diseases or interventions with a more informative body of evidence. If only studies with low reliability are identified, these may be presented in the rapid report as supplementary information. However, in order to be able to draw a conclusion about the relationship between the VoS and the quality of the treatment outcomes, further evidence must be consulted. In this case, or if no suitable studies have been identified, the transfer of evidence on the relationship between the VoS and the quality of treatment outcomes from another population or intervention to the one specified in the commission may be considered.

Clinical and procedural considerations regarding the specific population and/or intervention are always decisive when assessing the appropriateness of drawing a conclusion about the relationship between the VoS and the quality of treatment outcomes based on a transfer of evidence. It is therefore not possible to establish a universally applicable checklist. Only a list of potentially relevant criteria can be used. The individual criteria address various aspects that may be relevant when assessing transferability between populations and/or interventions and should then be taken into account accordingly. Transferability must be evaluated separately for each endpoint.

Information retrieval identified no documents that explicitly addressed the evaluation of transferability in the context of studies on the relationship between the VoS and the quality of treatment outcomes. Therefore, documents on transferability from other contexts, such as

systematic reviews, were used to develop the list of criteria. Fifteen documents were identified that mention criteria for the transfer of evidence. The criteria mentioned in the documents were extracted and compiled into a list of criteria for the research question of the rapid report.

The developed list included criteria on the following topics:

- Clinical picture and course of the disease
- Sociodemographic patient characteristics
- Disease-specific patient characteristics
- Making the diagnosis
- Comorbidities
- Intervention
- Implementation of the intervention
- Follow-up care
- Concomitant treatments
- Endpoints
- Specialization and experience of the treating staff
- Setting
- Additional criteria not included in the items above

The aim of using the criteria is to identify differences between populations and/or interventions that may be relevant to transferability. If such differences are identified, it must be assessed for each endpoint whether a transfer of the results, possibly with restrictions, is appropriate and to what extent they must be taken into account when interpreting the transferred results.

The selection of criteria and their assessment requires clinical and/or procedural expertise and should therefore generally be carried out with the involvement of clinical experts for both the target population/intervention and the population/intervention to be transferred. Furthermore, external evidence, for example in the form of systematic reviews, can be consulted to help decide which reference population(s) or intervention(s) are fundamentally suitable for transfer to the target population and intervention and, in the case of several suitable reference populations or interventions, which should be given priority.

Once one or more reference populations and interventions have been defined, comprehensive information retrieval is conducted for the respective reference populations

and interventions in accordance with the methodological approach for common diseases and interventions, and the relationship between the VoS and the quality of treatment outcomes is assessed.

Conclusion

This rapid report presents the development of a method to assess the relationship between the VoS and the quality of treatment outcomes for healthcare services used to treat rare diseases. The first step is always comprehensive information retrieval of studies on the given question. If no sufficiently informative studies are identified, a transfer from another population or intervention can be considered. To this end, it must be examined from which population and/or intervention this is reasonably possible.

Clinical and procedural considerations specific to the respective question are decisive when assessing transferability. A list of criteria was developed based on criteria for the transferability of evidence in other contexts. This list is intended to serve as a basis for weighing up differences between populations and interventions and for assessing transferability. This should generally be done with the involvement of clinical experts.

Once a population or intervention has been identified for the transfer of evidence, the relationship between the VoS and the quality of treatment outcomes can be examined for this population or intervention in accordance with the methods used in previous rapid reports with a sufficient body of evidence on the relationship between the VoS and the quality of treatment outcomes.

The method was developed based on literature concerning the transfer of evidence. No relevant documents containing methodological derivations of minimum volume requirements for rare diseases or requirements for hospital certification to treat specific rare diseases were identified. Likewise, no overarching methodological literature on minimum volumes for rare diseases was identified.

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AHRQ	Agency for Healthcare Research and Quality
AIHTA	Austrian Institute for Health Technology Assessment
CDA	Canada's Drug Agency
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information (German Institute for Medical Documentation and Information)
ERN	European Reference Networks for people with rare and complex diseases of low prevalence
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MVR	Minimum Volume Regulation
NAMSE	Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (National Action Alliance for People with Rare Diseases)
NARSE	Nationales Register für Seltene Erkrankungen (National Registry for Rare Diseases)
NICE	National Institute for Health and Care Excellence
SE-ATLAS	Versorgungsatlas für Menschen mit Seltenen Erkrankungen (Healthcare Atlas for People with Rare Diseases)
SGB	Sozialgesetzbuch (Social Code Book)
SIGN	Scottish Intercollegiate Guidelines Network
VoS	volume of services

1 Background

In Germany, the Federal Joint Committee (G-BA) has a legal mandate to set minimum volumes [1]. Hospitals are then generally only allowed to provide the corresponding healthcare service, i.e. intervention, if the hospital operator demonstrates annually that the set minimum volume will also be achieved in the following year.

The German Minimum Volume Regulation (MVR) is intended to help improve the quality of treatment outcomes by setting quantitative targets, particularly for the provision of complex, higher-risk services and procedures. By excluding the occasional provision of health care, patient safety is to be increased and the treatment risk minimized. This objective of the MVR has been confirmed several times by the verdicts of the Federal Social Court [2-4].

Therefore, in connection with quality assurance at approved hospitals, the G-BA decides on a catalogue of elective services for which the quality of treatment outcomes depends on the volume of services (VoS) provided and sets minimum volumes for the respective services per doctor and/or hospital location. The legal basis for this is §136b (1), Sentence 1, No. 2 of the Fifth Book of the Social Code (SGB V) [5]. The setting of a specific minimum volume is preceded by an assessment of the dependence of the quality of treatment outcomes on the VoS provided. As a basis for its decision, the G-BA regularly commissions the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the relationship between the VoS and the quality of treatment outcomes for certain higher-risk services or procedures on the basis of relevant studies.

To date, no MVR has been established in Germany for higher-risk services for rare diseases. In the European Union, a disease is considered rare if it affects fewer than 5 in 10,000 people [6].

Rare diseases are not exempt from the requirement to set minimum volumes for higher-risk services and procedures in order to minimize risks to patients that may arise from providing occasional health care.

Due to the low frequency of these services and procedures, a low number of cases per hospital is to be expected for higher-risk services and procedures for rare diseases, especially if they are performed on a decentralized basis. If the doctors who perform these procedures do not perform them for different hospitals in a specific catchment area, a low number of cases per doctor is also to be expected. It should be noted that the problem of low case numbers, depending on the frequency of the rare disease in question, may remain even despite measures to prevent the occasional provision of health care (centralization, doctors who perform procedures for different hospitals in a defined catchment area).

The use of analyses to examine the relationship between the VoS and the quality of treatment outcomes requires standardized treatment [7]. In addition, it may be necessary to decide whether the VoS at the hospital level or the VoS at the doctor level is the decisive factor. If the treatment requires a longer stay in hospital or a greater demand for inpatient services, such as more intensive care, the importance of the VoS at the hospital level increases [8]. However, if the treatment requires, for example, a higher level of surgical skill on the part of the surgeon, the VoS at the doctor level is the decisive factor [8].

In addition to the low number of cases, in the case of rare diseases, the code used for coding diagnoses in outpatient and inpatient care, which is often based on the German modification of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM), can pose a challenge for the use of data in studies on the relationship between the VoS and the quality of treatment outcomes. Rare diseases are often grouped together or coded in a non-specific manner using the ICD-10-GM classification [9]. In addition, the use of surgical procedure coding for analysis purposes can be challenging if it is not done using a code specific to the rare disease, but rather a general code [10]. Conducting studies based on hospital billing data is therefore often difficult for rare diseases. The use of such data may involve additional inaccuracy if the service is provided by a specialized external professional called in by the hospital or if the surgical procedure is performed in another hospital.

No provable causal relationship between the VoS provided and the quality of treatment outcomes is required to set a minimum volume. However, there must be evidence indicating a probable relationship [11]. Due to the low number of cases in rare diseases, the question arises as to what evidence body is required for such an indication. The low number of cases involving higher-risk services and procedures for rare diseases, whether due to a decentralized healthcare landscape and/or a very low prevalence even for rare diseases, makes it difficult to conduct scientific studies on the relationship between the number of cases and the quality of treatment outcomes, as such studies require at least some hospitals to have a high number of cases. It is therefore to be expected that no or very few suitable studies can be identified. On this basis, a potential relationship between the VoS and the quality of treatment outcomes can only be demonstrated through the (further) development of specific methods, such as the transfer of results from studies on different populations or procedures to the respective rare disease.

2 Research question

The aim of this investigation is to develop a method for assessing the relationship between the VoS and the quality of treatment outcomes for healthcare services used to treat rare diseases with correspondingly low case numbers and an insufficient body of evidence.

3 Course of the project

On 9 October 2024, the G-BA commissioned IQWiG to describe in a scientific report whether, and if so how, a methodological assessment[3] of the relationship between the VoS and the quality of treatment outcomes can also be performed for healthcare services used to treat rare diseases with correspondingly low case numbers and an insufficient body of evidence. This assessment is necessary for setting minimum volumes.

A rapid report was prepared on the basis of an internal project outline. This was submitted to the G-BA and published on the IQWiG website four weeks later.

[3] in accordance with §136b (1), Sentence 1, No. 2, SGB V

4 Methods

The present commission comprises the development of options for assessing the relationship between the VoS and the quality of treatment outcomes in rare diseases. This development was supported by information retrieval and assessment.

The following aspects were addressed:

- Identification of methodological derivations of minimum volume requirements for rare diseases from other countries, as well as requirements for hospital certification to treat specific rare diseases
- Identification of overarching methodological literature on minimum volumes for rare diseases
- Identification of methodological literature on the transferability of study results to other populations/interventions

4.1 Information retrieval

The exploratory information retrieval for this commission covered:

- Previous methodological work at the Institute on the transferability of study results to other populations/interventions, as well as on minimum volumes
- Literature search for methodological documents in MEDLINE
- Website search for methodological documents on the above topics from other HTA agencies (NICE, AHRQ, CDA, JohannaBriggs, SIGN, and AIHTA) and certification bodies
- Additional search techniques:
  - Reviewing reference lists of the identified methodological documents
  - Use of the "Cited Reference" function in Semantic Scholar and the "Similar Articles" function in PubMed based on previously identified methodological documents

Selection of relevant studies or documents

The search for and selection of methodological documents was carried out by one person. The quality of the results was assured by a second person. The documentation in the rapid report is limited to the presentation of the specific results.

4.2 Methodological components

The following methodological approach was developed.

- Formulation of key points regarding the transferability of results on relationships between the VoS and the quality of treatment outcomes between populations and/or interventions
- Other methodological aspects that were identified in the course of the project:
  - General approach for examining the relationship between the VoS and the quality of treatment outcomes in rare diseases
  - Dealing with studies of limited reliability that examine the relationship between the VoS and the quality of treatment outcomes for the population and intervention covered by the commission

5 Results

5.1 Information retrieval

5.1.1 Methodological derivations of minimum volume requirements for rare diseases from other countries, as well as requirements for hospital certification to treat specific rare diseases

No relevant documents containing methodological derivations of minimum volume requirements for rare diseases or requirements for hospital certification to treat specific rare diseases were identified.

5.1.2 Overarching methodological literature on minimum volumes for rare diseases

No relevant overarching methodological literature on minimum volumes for rare diseases was identified.

5.1.3 Identification of methodological literature on the transferability of study results to other populations/interventions

The documents identified during the exploratory literature search for methodological work were reviewed. A total of 15 documents contained criteria for assessing transferability between populations or interventions. These documents are presented in the following Table 1.

Table 1: Pool of included documents with criteria for assessing transferability (multipage table)

Document (abbreviation)	Organization	Title
Atkins 2011 [12]	Agency for Healthcare Research and Quality (AHRQ)	Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program
Baxter 2019 [13]	-	Towards greater understanding of implementation during systematic reviews of complex healthcare interventions: the framework for implementation transferability applicability reporting (FITAR)
Bornhöft 2006 [14]	-	Checklist for the qualitative evaluation of clinical studies with particular focus on external validity and model validity
CASP 2018 [15]	Critical Appraisal Skills Programme	Critical Appraisal Skills Programme: making sense of evidence. 12 questions to help you make sense of a cohort study
Dekkers 2010 [16]	-	How to assess the external validity of therapeutic trials: a conceptual approach
Dumortier 2021 [17]	-	Exposure-response modeling for extrapolation from adult to pediatric patients who differ with respect to prognostic factors: Application to everolimus

Table 1: Pool of included documents with criteria for assessing transferability (multipage table)

Document (abbreviation)	Organization	Title
Ekkernkamp 2003 [18]	-	Methodology manual for "HTA fast-track procedures" and exemplary "short HTA": The role of quantitative ultrasound procedures in determining the risk of osteoporotic fractures
EMA ICH 2025 [19]	European Medicines Agency (EMA)	ICH guideline E11A on paediatric extrapolation - Scientific guideline
EMA 2018 [20]	European Medicines Agency	Reflection paper on the use of extrapolation in the development of medicines for paediatrics
EUnetHTA 2011 [21]	European Network for Health Technology Assessment (EUnetHTA)	Adapting existing HTAs from one country into other settings
Guyatt 2011 [22]	Grading of Recommendations Assessment, Development and Evaluation (GRADE)	GRADE guidelines: 8. Rating the quality of evidence – indirectness
Ludwig Boltzmann Institute 2007 [23]	Ludwig Boltzmann Institute HTA (now AIHTA)	(Internal) Manual – Procedures and Methods, Part 2
Munthe-Kaas 2019 [24]	-	Systematic mapping of checklists for assessing transferability
SIGN 2019 [25]	Scottish Intercollegiate Guidelines Network (SIGN)	SIGN 50 – A guideline developer's handbook
Weise 2020 [26]	-	Assessing context suitability (generalizability, external validity, applicability or transferability) of findings in evidence syntheses in healthcare – An integrative review of methodological guidance
AHRQ: Agency for Healthcare Research and Quality; AIHTA: Austrian Institute for Health Technology Assessment; EMA: European Medicines Agency; EUnetHTA: European Network for Health Technology Assessment; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: health technology assessment; SIGN: Scottish Intercollegiate Guidelines Network		

5.2 Results on methodological components

For the treatment of specific rare diseases, no methodological derivations of minimum volume requirements from other countries or requirements for hospital certification were identified. Likewise, no overarching methodological literature on minimum volumes for rare diseases was identified. The approach described below for investigating the relationship between the VoS and the quality of treatment outcomes in rare diseases was therefore developed on the basis of the identified methodological literature on the transferability of study results to other populations/interventions.

Approach to investigating the relationship between the VoS and the quality of treatment outcomes in rare diseases

In accordance with the approach outlined in Figure 1, information retrieval is the first step in processing commissions on IQWiG assessments of the relationship between the VoS and the quality of treatment outcomes for certain higher-risk interventions. This consists of focused information retrieval of systematic reviews and comprehensive information retrieval of suitable studies. The studies must meet pre-specified inclusion criteria. While the inclusion criteria ensure that the study results are fundamentally usable, a detailed analysis of the internal validity of the included studies is carried out in a later assessment step.

Due to the framework conditions described in Chapter 1, it must be assumed that information retrieval within the scope of commissions on assessments of the relationship between the VoS and the quality of treatment outcomes in rare diseases will not regularly identify any published study results. In the event that studies are identified, the reliability of the results should be critically examined. In the context of rare diseases, reliability may be further limited for the following reasons in particular:

- **Lack of precision due to insufficient sample sizes**
  Smaller sample sizes lead to lower precision and thus to broader confidence intervals around an effect estimate. This can make it more difficult to demonstrate a relationship between the VoS and the quality of treatment outcomes for interventions in rare diseases. This is even more true if the quality endpoint being examined is a rare event.
- **Inaccuracies in the billing data used**
  In studies based on an analysis of billing data, it should be noted that these data are often incomplete or inaccurate, as they were collected for billing purposes rather than for research [27,28]. These shortcomings in documentation, for example with regard to risk factors and patient history, can have a greater impact in rare diseases due to the small sample sizes and lead to a loss of precision [27,28] due to incorrect data or cases that cannot be analysed. Another inaccuracy in the billing data used can occur when a doctor specializing in the specific rare disease performs the intervention at several hospitals. In this case, the billing data at the hospital level do not reflect the doctor's experience.
- **Inaccuracies in the coding of rare diseases**
  In health data recorded in Germany prior to 2023, rare diseases are often not specifically identifiable. In the ICD-10-GM classification, less than 10% of rare diseases are represented by a specific diagnosis code [29]. Rare diseases are often only coded using ICD-10-GM in a group of similar diseases, which are also usually more common [30]. For a more specific classification, the Orphanet nomenclature for rare diseases was developed at the European level [31]. Based on these Orpha codes, the former German

Institute for Medical Documentation and Information (DIMDI) developed the Alpha-ID-SE file. This file contains more than 15,000 diagnostic names of rare diseases linked to Orpha identification numbers, with most rare diseases having several diagnosis names. With the help of the Alpha-ID-SE file, healthcare providers can standardize and simplify the coding of rare diseases using ICD-10-GM and Orpha identification numbers. Since 2023, the use of ICD-10-GM coding in combination with the Orphanet nomenclature has been mandatory for the clear coding of rare diseases in the inpatient sector [29]. In studies in people with a rare disease in the German healthcare context that are based on the analysis of billing data and analyse data from a period that at least partially predates the introduction of mandatory coding via the Alpha-ID-SE file, the informative value of the results must therefore be questioned. For studies that use data from other countries, it must be examined on a case-by-case basis to what extent the rare disease can be clearly identified based on the codes and selection criteria used.

If studies are identified that are sufficiently reliable, the approach will be the same as in previous rapid reports on the relationship between the VoS and the quality of treatment outcomes.

If studies are identified that are not sufficiently reliable to draw conclusions from them alone, but are also not so unreliable that the results must be classified as unusable, the results of these studies are presented as supplementary information. However, further evidence must be consulted in order to draw conclusions about the relationship between the VoS and the quality of treatment outcomes.

If no suitable studies are identified that are sufficiently reliable to draw conclusions about the relationship between the VoS and the quality of treatment outcomes from them alone, an attempt is made to draw on further evidence. To this end, evidence on the relationship between the VoS and the quality of treatment outcomes from another population or intervention may be transferred to the one specified in the commission.

Definition of transferability

The population specified in the respective commission is referred to below as the target population, while the population from which evidence is to be transferred to the target population is referred to as the reference population. Similarly, the healthcare services are referred to as the reference intervention and target intervention. The reference question refers to the combination of the reference population and reference intervention, while the target question is defined analogously.

Various terms are used in the literature in connection with the transferability of evidence [12]: applicability, external validity, generalizability, directness/indirectness, and relevance. The term "transferability" is used below.

There are a number of different definitions for the terms mentioned (see, for example,[12] and [22]). In the context of this rapid report, transferability is defined as the extent to which the relationship between the VoS and the quality of treatment outcomes observed for the reference population remains when the target population differs from the reference population and/or when the target intervention differs from the reference intervention.

General approach used in the project

The general approach for investigating the relationship between the VoS and the quality of treatment outcomes in rare diseases is shown in Figure 1. The literature search for the target question as well as the identification of a potential reference population/intervention and its review for transferability, and the related exploratory searches can be carried out in parallel if necessary.

The focused search for systematic reviews as part of the work on the question covered by the commission also serves to identify external evidence that can be used to determine a potential reference population/intervention. Another basis for deciding on a potential reference population/intervention is consultation with clinical experts for the rare disease and, if necessary, clinical experts for the potential reference population/intervention. Furthermore, exploratory searches should be conducted before determining the reference population/intervention in order to estimate the success of comprehensive information retrieval.

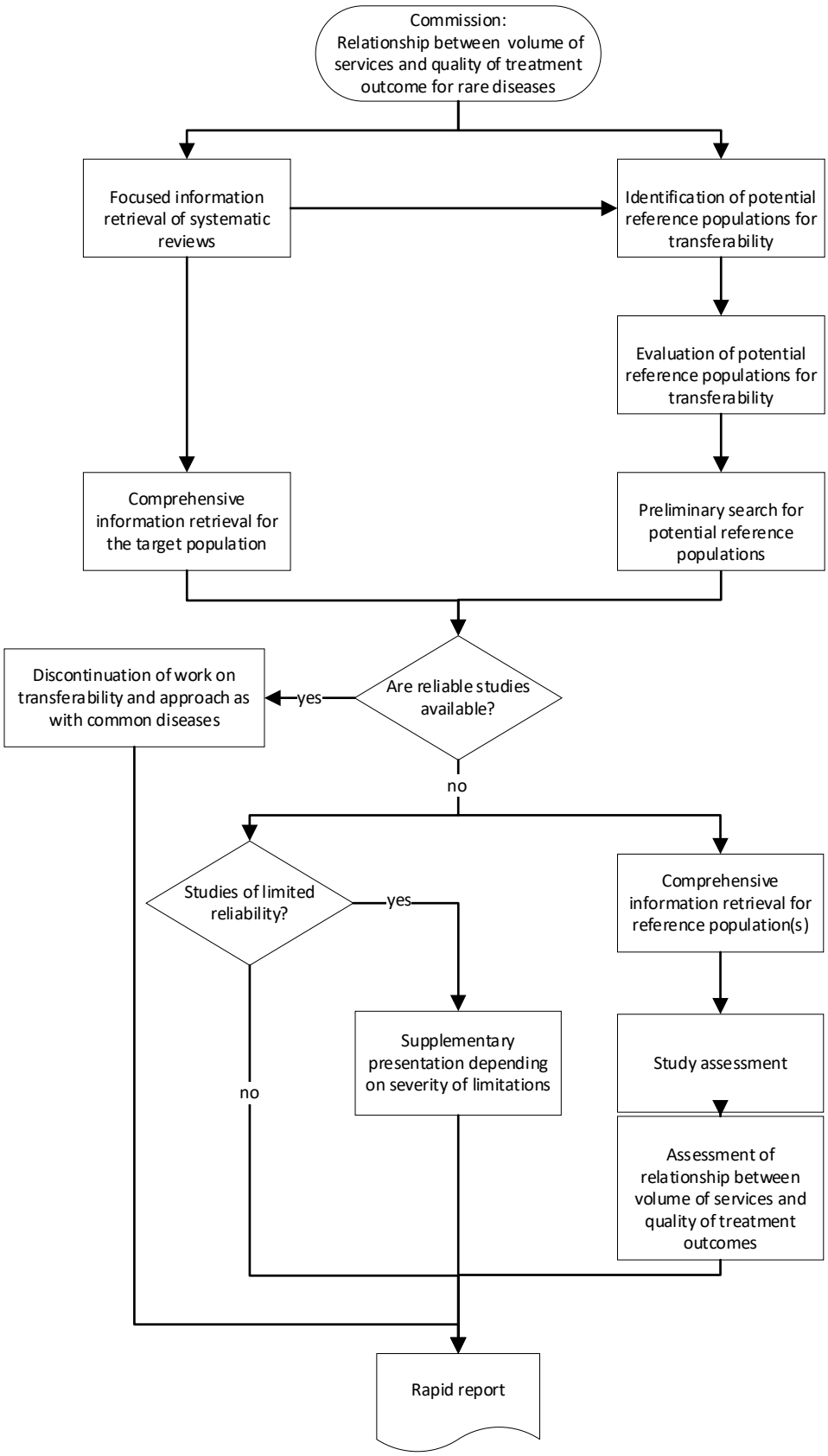

Figure 1: Approach for assessing the relationship between the VoS and the quality of treatment outcomes in rare diseases

5.2.1 Assessment of transferability

Clinical and procedural considerations regarding the specific population and/or intervention are always decisive when assessing the appropriateness of transferring a conclusion on the relationship between the VoS and the quality of treatment outcomes from a reference population to the target population or from a reference intervention to the target intervention. It is therefore not possible to establish a universally applicable checklist of criteria that would allow transfer from a reference question to a target question. It is only possible to establish criteria that need to be examined to determine whether they differ between the reference question and the target question and to what extent this allows or prevents transfer of the results.

The extent to which transfer between the reference question and the target question is possible must be assessed separately for each endpoint. For example, it is conceivable that all-cause mortality is transferable from the reference intervention to the target intervention within the same disease, while the occurrence of certain complications, the frequency of which is associated with the rare disease itself, is not transferable.

Even though it is not possible to create a universally applicable checklist of criteria, we compiled a list of criteria that may be relevant and should be considered when assessing the transferability of results on the relationship between the VoS and the quality of treatment outcomes between interventions or populations (see Section 5.2.1.2).

5.2.1.1 Characteristics of the documents included

During information retrieval, no documents were identified that explicitly addressed the assessment of transferability in the context of studies on the relationship between the VoS and the quality of treatment outcomes. Therefore, the list of criteria was developed based on studies on the transferability of evidence in the context of clinical trials and cohort studies, as well as on the transferability of evidence from adults to children and between healthcare systems. Table 2 summarizes the characteristics of the documents used to develop the list of criteria.

Table 2: Characteristics of the documents containing criteria for transferability (multipage table)

Document	**Scope**	**Transfer:** ▪ **Reference** ▪ **Target**	**Terminology for transferability and definition, if applicable (original wording)**
Atkins 2011	Assessment of the applicability of findings from clinical studies in the preparation of systematic reviews	▪ Study population ▪ Population of interest	**Applicability**: The extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention is applied to the population of interest under "real-world" conditions. [Page 1199]
Baxter 2019	When preparing systematic reviews, recording and analysing factors that are important for the transferability of complex health interventions	▪ Study context ▪ Specific application or decision context	**Transferability:** However, “generalisability” (synonymous with external validity) is usually used to refer to whether the results of a study might be relevant to other general sites and populations. Whereas “applicability” typically refers to feasibility and process, providing insights into whether and how an intervention may be implemented elsewhere in a particular context. The term "transferability" is similar to "generalisability" in referring to the likelihood of replication of outcomes, but in common with applicability, it is distinguished from generalisability by relating to outcomes in a specific context. [Page 2]
Bornhöft 2006	Assessment of the external validity of clinical studies in the study planning process or in the preparation of systematic reviews	▪ Study population ▪ General population	**External validity**: The extent to which the effects observed in a study truly reflect what can be expected in a target population beyond the people included in the study, which includes the possibility to transfer and apply study results to a distinct population / decision and patient's situation. [Page 3]
CASP 2018	Assessment of cohort studies	▪ Cohort study ▪ Local context	Will the results help locally? [Page 6]
Dekkers 2010	Assessment of the external validity of the results of clinical studies on therapeutic interventions	▪ Study population ▪ People who do not belong to the study population	**External validity**: External validity will be used to denote the question of whether the study results are valid for patients other than those in the original study population in a treatment setting that is in all respects equal to the treatment setting of the original study. **Applicability**: We refer to applicability as the question of whether study results are valid for patients to whom results are generalizable but who are in a different treatment setting than the original study population. [Page 90]

Table 2: Characteristics of the documents containing criteria for transferability (multipage table)

Document	**Scope**	**Transfer:** ▪ **Reference** ▪ **Target**	**Terminology for transferability and definition, if applicable (original wording)**
Dumortier 2021	Extrapolation of the exposure-response relationship of drugs for adults to paediatric patients	▪ Adults ▪ Children	**Paediatric extrapolation:** Paediatric extrapolation is an approach encouraged by the health authorities to evaluate the efficacy of a drug in children that reduces the amount of paediatric efficacy data required. It requires assumptions relating the exposure-response relationship in adult and paediatric populations, which accounts for those risk factors that differ between the two populations. [Page 597]
Ekkernkamp 2003	Assessment of the transferability of international/foreign study results to the German healthcare system in the context of HTA reports	▪ Foreign study results ▪ German context	**External validity:** Assessment of the transferability of study or review results under the above-mentioned aspects* to the specific decision-making situation [page 59] *the intervention/technology of interest, the system- and indication-related application situation, and the patient or client groups affected, the desired outcome parameters
EMA ICH 2025, EMA 2018	Paediatric extrapolation to support the development and approval of paediatric medicines	▪ Reference population (adults) ▪ Children	**Paediatric extrapolation:** An approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease* and the expected response to a medicinal product would be sufficiently similar in the paediatric [target] and reference (adult or other paediatric) population. [Page 5] * For the purposes of this document, "disease" includes both "diseases" and "conditions."
EUnetHTA 2011	Assessment of the relevance, reliability, and transferability of data/information from an HTA report from another context with regard to one's own national/regional context	▪ Foreign HTA report ▪ National/regional context	**Transferability:** For the WP5 toolkit, transferability is about the ability to apply information from one report into a user's target setting. Each domain of the WP5 toolkit includes transferability questions and links to relevant resources; the purpose being to help the user decide whether they can adopt, need to adapt, or disregard specific pieces of information when applying these to their target setting. [Page 44]

Table 2: Characteristics of the documents containing criteria for transferability (multipage table)

Document	**Scope**	**Transfer:** ▪ **Reference** ▪ **Target**	**Terminology for transferability and definition, if applicable (original wording)**
Guyatt 2011	Assessment of the indirectness of clinical research results in the context of systematic reviews or clinical guidelines	▪ Study population ▪ Population of interest, or ▪ Similar intervention ▪ Intervention of interest, or ▪ Surrogate endpoint ▪ Endpoint of interest, or indirect comparisons	**Indirectness:** First, patients may differ from those of interest (the term applicability is often used for this form of indirectness). Secondly, the intervention tested may differ from the intervention of interest. Decisions regarding indirectness of patients and interventions depend on an understanding of whether biological or social factors are sufficiently different that one might expect substantial differences in the magnitude of effect. Thirdly, outcomes may differ from those of primary interest – for instance, surrogate outcomes that are not themselves important, but measured in the presumption that changes in the surrogate reflect changes in an outcome important to patients. A fourth type of indirectness, conceptually different from the first three, occurs when clinicians must choose between interventions that have not been tested in head-to-head comparisons. [Page 1303]
Ludwig Boltzmann Institute 2007	Assessment of external validity in the preparation of systematic reviews in the HTA context	▪ Individual study ▪ Question addressed by a systematic review	**External validity (generalizability)**: External validity depends primarily on the population and the healthcare system and is therefore a subjective assessment (is the study relevant to "my" population, to "my" healthcare system?). In intervention studies, however, there are essential aspects of study design that can influence external validity. [Page 41]
Munthe-Kaas 2019	Assessment of the transferability of study results in the context of systematic reviews in the health and social sector	▪ Systematic review ▪ Specific setting	**Transferability**: Whether the level of effectiveness (or perceptions and experiences) of an intervention in a specific setting or population will be similar to the observed level of effectiveness (or perceptions and experiences) observed in a systematic review. [Page 2]
SIGN 2019	Assessment of the applicability of foreign/international study results in the development of guidelines in the Scottish healthcare system	▪ Results of foreign studies ▪ NHS Scotland	**Applicability**: This is often referred to as directness of evidence, but can also be referred to as applicability or external validity. In this context, it relates to how directly applicable the evidence is to NHS Scotland. [Page 21]

Table 2: Characteristics of the documents containing criteria for transferability (multipage table)

Document	**Scope**	**Transfer:** ▪ **Reference** ▪ **Target**	**Terminology for transferability and definition, if applicable (original wording)**
Weise 2020	Methodological recommendations for assessing the contextual suitability of evidence on the effectiveness of healthcare interventions in the context of HTA reports and systematic reviews	▪ Study context ▪ Specific application or decision context	**Context suitability:** According to the definitions of Burford and colleagues, researchers may assess whether the results provide a correct basis for generalizations to other circumstances (generalizability/external validity), whether it is feasible to implement an intervention in a specific context (applicability), or whether a similar level of effectiveness could be achieved if an intervention were implemented in another specific context (transferability). To summarize these concepts and associated terms, we use context suitability as a generic term in the following. [Page 761]
CASP: Critical Appraisal Skills Programme; EMA: European Medicines Agency; EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; SIGN: Scottish Intercollegiate Guidelines Network; NHS: National Health Service; WP5: Work Package 5			

5.2.1.2 List of criteria

The criteria for the transferability of evidence listed in the documents in Table 1 were compiled and reviewed for their relevance in the specific context of assessing the relationship between the VoS and the quality of treatment outcomes in rare diseases. The relevant criteria were then grouped by content, summarized where possible, and adapted to the context of this rapid report.

The list is a comprehensive collection of criteria that may be relevant when assessing transferability in the context of assessing the relationship between the VoS and the quality of treatment outcomes. It supports decision-making. To assess transferability for a specific question, it is not necessary to answer for each individual criterion whether there are differences between the reference question and the target question with regard to this criterion. Furthermore, a difference does not immediately mean that transfer from the reference question to the target question is not possible. Possible effects of differences are described in Section 5.2.1.3.

The following list of criteria was developed.

5.2.1.2.1 Clinical picture and course of the disease

Are there differences in the clinical picture between the reference population and the target population? Differences in the following aspects, for example, may be relevant here:

- Aetiology
- Manifestations of the disease
- Method of measuring the manifestations of the disease

It should also be examined whether there are differences in the course of the disease between the reference population and the target population, for example:

- in the course of the disease until the intervention is received
- in the expected course of the disease without intervention
- in the factors influencing the course of the disease

There may also be relevant subtypes of the diseases in the reference or target population. If so, it must be clarified whether the results can be transferred between all subtypes or whether the reference or target population must be restricted to certain subtypes.

The complete list of criteria on the clinical picture, as compiled from the documents, can be found in Appendix A, Table 3.

5.2.1.2.2 Sociodemographic patient characteristics

Do the reference population and the target population differ in terms of the sociodemographic characteristics of the patients? The following characteristics may be relevant:

- Age and maturity
- Sex
- Height, weight, BMI
- Ethnicity
- Geographical aspects
- Socioeconomic aspects
- Lifestyle factors such as smoking or physical activity

The complete list of criteria on sociodemographic patient characteristics, as compiled from the documents, can be found in Appendix A, Table 4.

5.2.1.2.3 Disease-specific patient characteristics

Do the reference population and the target population differ in terms of disease-specific patient characteristics? The following characteristics may be relevant:

- Severity or stage of the disease
- Prognostic factors or other treatment-relevant factors that influence the relationship between the VoS and the quality of treatment outcomes
- Age at the time of diagnosis
- Age- or maturation-related differences in symptoms
- Duration of the disease up to the time of intervention
- Biomarkers that reflect the severity or progression of the disease
- Genetic characteristics

The complete list of criteria on disease-specific patient characteristics, as compiled from the documents, can be found in Appendix A, Table 5.

5.2.1.2.4 Making the diagnosis

- Are there differences in making the diagnosis between the reference population and the target population?

- Do the qualifications, specialization, and experience of the persons heavily involved in making the diagnosis differ between the reference and target questions?

The complete list of criteria on making the diagnosis, as compiled from the documents, can be found in Appendix A, Table 6.

5.2.1.2.5 Comorbidities

Do the patients in the reference population or the patients receiving the reference intervention differ from those in the target population or those receiving the target intervention in terms of the spectrum of comorbidities?

The complete list of criteria on comorbidities, as compiled from the documents, can be found in Appendix A, Table 7.

5.2.1.2.6 Intervention

Do the reference population and the target population differ in terms of the intervention? Differences in the following aspects may be relevant here, for example:

- Complexity of the intervention
- How long the intervention has been implemented
- Materials used

If newer interventions have replaced older ones, it is important to consider which ones are suitable for transfer and which are not. The inclusion and exclusion criteria for the reference question may need to be formulated accordingly in order to include only those interventions that are classified as transferable.

The complete list of criteria on the intervention, as compiled from the documents, can be found in Appendix A, Table 8.

5.2.1.2.7 Implementation of the intervention

Are there differences in the implementation of the intervention? Differences in the following aspects may be relevant here, for example:

- Technology used
- The state of development of the technologies used
- Duration of treatment
- Availability of technologies or resources

- Organ(system) treated, possibly also differences due to growth or maturation processes that complicate or simplify the implementation of the intervention

The complete list of criteria on the implementation of the intervention, as compiled from the documents, can be found in Appendix A, Table 9.

5.2.1.2.8 Follow-up care

Are there differences in follow-up care? Differences in the following aspects may be relevant here, for example:

- Intensity of follow-up care
- Expected adherence to follow-up care
- Qualifications of the persons performing follow-up care

The complete list of criteria on follow-up care, as compiled from the documents, can be found in Appendix A, Table 10.

5.2.1.2.9 Concomitant treatments

Are there differences in previous or concomitant treatments? Differences in the following aspects may be relevant here, for example:

- Are the previous or concomitant treatments used as a standard?
- Necessity of certain previous or concomitant treatments
- Availability and range of previous or concomitant treatments
- Treatment with the same intervention in the past

The complete list of criteria on concomitant treatments, as compiled from the documents, can be found in Appendix A, Table 11.

5.2.1.2.10 Endpoints

Are there differences between the endpoints relevant for the target question and those expected for the reference question in the corresponding studies? Differences in the following aspects may be relevant here, for example:

- Expected treatment outcomes
- Expected event rates for event-based endpoints:
  It is unfavourable, for example, if a certain complication is not expected at all or only very rarely in the reference population. This would not be covered if the results were transferred, so it would be possible that for this endpoint with regard to the target

question, there is a clear relationship between the VoS and the quality of treatment outcomes, but this is not investigated in studies on the reference question. If this applies to a central endpoint, transfer from another reference population or intervention should be considered.

- Expected symptoms of side effects or complications:
  If possible complications or side effects manifest themselves in different symptoms, it may be difficult to assign the results to be transferred.
- Times at which endpoints should be recorded (for example, after a certain period following the intervention)
  Are there differences in the times at which complications are expected, for example? This must be taken into account when interpreting the results. It should be noted in particular that, due to growth and maturation processes, different follow-up periods may be appropriate for long-term events in children than in adults.
- Qualifications, specialization, and experience of the persons recording the endpoints

The complete list of criteria on concomitant treatments, as compiled from the documents, can be found in Appendix A, Table 12.

5.2.1.2.11 Specialization and experience of the treating staff

Are the qualifications, specialization, and experience of the treating staff comparable between the reference population/intervention and the target population/intervention? To assess the comparability of qualifications and specialization, the (model) continuing education regulations of the German Medical Association [32] can be used, for example.

The complete list of criteria on the specialization and experience of the treating staff, as compiled from the documents, can be found in Appendix A, Table 13.

5.2.1.2.12 Setting

Are there any differences between the reference question and the target question with regard to the setting? Differences in the following aspects may be relevant here, for example:

- Healthcare context
- Processes used
- Conditions under which the intervention is carried out
- Preparation for the intervention
- Availability of technologies and resources

In addition, it should be noted whether the time restrictions set for the inclusion of studies on the target question are the same for the reference question, or whether the corresponding inclusion criterion needs to be adjusted. Have procedures changed at the same time, or was a procedure introduced at different times in both populations, for example?

The complete list of criteria on the setting, as compiled from the documents, can be found in Appendix A, Table 14.

5.2.1.2.13 Additional criteria

Are there other reasons to assume that the relationship between the VoS and the quality of treatment outcomes is different for the reference question than for the target question?

5.2.1.3 Dealing with the identified differences

The list of criteria is first used to define a suitable reference population or intervention. This list can also be used to check the studies identified in information retrieval for the reference question with regard to transferability.

Determining the reference population

For all differences that were identified using the list of criteria and that are considered relevant to the transfer situation, it must be determined for each endpoint relevant to the target question what the differences mean for the transferability of a relationship between the VoS and the quality of treatment outcomes. The following options can be considered:

- The differences are so severe that transfer is not meaningful.
- The differences are relevant, but can be reduced to a negligible level by further restrictions regarding the reference population and/or intervention. The results for the restricted reference question are transferable to the target question.
- The differences are relevant if transfer to the entire target population is desired. However, there is a subpopulation for which the differences are not relevant. The reference results can be transferred to this subpopulation to answer the target question.
- The differences are relevant and cannot be eliminated by further restrictions on the reference population and/or intervention. However, it is possible to estimate how they influence the relationship between the VoS and the quality of treatment outcomes. This means that the results can be transferred, at least to a limited extent. It should be specified in advance how a transfer is valid and how this should be taken into account when interpreting the results. With regard to the specialization of the treating staff, it could be argued here that if a relationship in favour of higher VoS for the more specialized treating staff is found, this relationship probably also exists for the less specialized treating staff. Conversely, it may be reasonable to assume that a relationship

in favour of higher VoS for less specialized treating staff cannot be readily transferred to more specialized treating staff.

- The differences have no relevant influence on the relationship between the VoS and the quality of treatment outcomes. It is possible to transfer the results from the reference question to the target question.

Examination at the level of individual studies

After information retrieval for the reference question, transferability must be examined for the individual studies both as a whole and at the level of the endpoints considered. Possible results are:

- The differences are so severe that the study or individual endpoints considered in the study are excluded.
- The differences are relevant, but it is possible to estimate how they influence the relationship between the VoS and the quality of treatment outcomes. The transfer of results to the study or endpoint level is possible, at least to a limited extent.
- The differences have no relevant influence on the relationship between the VoS and the quality of treatment outcomes. The results can be transferred at the study or endpoint level.

5.2.2 Involvement of experts

The criteria compiled in Section 5.2.1.2 do not constitute a universally applicable and complete checklist for determining whether it is appropriate to transfer evidence from a reference population or intervention to the target population or intervention. Clinical and/or procedural expertise is required to determine which criteria are relevant to the question at hand and must be used to assess transferability. The selection of criteria and their assessment should be carried out with the involvement of clinical experts for the rare disease and the therapeutic intervention covered in the commission.

5.2.3 Transfer of results

Once one or more reference populations and interventions have been defined, the relationship between the VoS and the quality of treatment outcomes is then assessed for these populations/interventions in accordance with the methods used in previous rapid reports on such questions in the context of non-rare diseases. Comprehensive information retrieval is performed for the reference question(s) and the internal validity of the studies is assessed. If a transfer is only valid with restrictions (see Section 5.2.1.3), this is taken into account in the conclusions on the derivation of a relationship between the VoS and the quality of treatment outcomes for the target question.

A mathematical transfer of an effect in the form of a conversion for another population, for example using propensity score methods as proposed by Cole et al. [33] and Stuart et al. [34], is only possible if individual patient data are available for at least the target population. Based on experience, this is not to be expected in studies on the relationship between the VoS and the quality of treatment outcomes. If suitable data are available for a particular question, it must nevertheless first be examined at the clinical and procedural level to what extent a transfer of results is meaningful, because only then can the conversion of an effect lead to usable results. However, it should be noted that these methods are based on additional assumptions, some of which cannot be verified. This means that the transferred results are subject to further uncertainties in addition to the uncertainty caused by the indirect nature of the data. Converting effects is only meaningful if the results are nevertheless sufficiently reliable to allow conclusions to be drawn about the relationship between the VoS and the quality of treatment outcomes.

5.2.4 Studies with limited reliability when compared with the results after transfer

If, when assessing the relationship between the VoS and the quality of treatment outcomes for a rare disease, studies are identified that meet the inclusion criteria for the target question in all respects except for the statistical models used, these may be presented as supplementary information, depending on the severity of the violation of the following modelling criteria.

No adjustment for cluster effects

If the presence of cluster effects at the hospital level is not taken into account in the analysis, this does not distort the effect estimate, but leads to an overly optimistic evaluation of statistical accuracy. This means that the point estimators are valid, but the confidence intervals or p-values are excessively narrow or small to an unknown extent. Therefore, it is not possible to estimate the statistical significance of the estimated effects. Nevertheless, the point estimates can be compared with the transferred results. If this reveals extensive – in particular qualitative - deviations, this could indicate a lack of transferability.

No adjustment for risk factors

A lack of adjustment for risk factors can result in biased effect estimates. If the direction and extent of the bias can be estimated, these results may still provide indications of the extent to which the unadjusted effect estimates for the target population/intervention are compatible with the transferred effect estimates.

Use of unsuitable models

When using unsuitable models, it must be examined on a case-by-case basis to what extent the results can still be used to draw conclusions about the adequacy of the transfer in comparison with the transferred results.

6 Discussion

The aim of this investigation was to develop a method for assessing the relationship between the VoS and the quality of treatment outcomes for healthcare services for rare diseases with correspondingly low case numbers. The difficulty of the topic is evident, among other things, in the fact that an exploratory search for international literature did not identify any documents on methodological derivations of minimum volume requirements for rare diseases or on hospital certification criteria for treating specific rare diseases. Likewise, no overarching methodological literature on minimum volumes for rare diseases was identified.

In order for the G-BA to be able to set a minimum volume for a service, the service must be eligible for minimum volumes in accordance with the G-BA's rules of procedure [7]. This means, among other things, that there must be a relationship between the quality of treatment outcomes and the VoS provided. Accordingly, in the case of services for rare diseases, this relationship should also be examined in accordance with the method developed by IQWiG [35]. In this rapid report, we propose the transfer of evidence only in cases where no sufficiently reliable studies can be identified. This is based on the assumption that there are reference populations or interventions that can be considered sufficiently similar to the population and intervention covered by the commission or for which the same skills and structures are required. It is then likely that a relationship between the VoS and the quality of treatment outcomes that exists for the reference population or intervention also applies to the population and intervention covered by the commission. Due to the indirect evidence, this transfer leads to a loss of certainty of conclusions, but nevertheless offers a possibility to draw a conclusion as to whether a minimum volume can also lead to an improvement in healthcare for a rare disease.

Assessing the transferability from a reference population/intervention to a target population/intervention requires clinical expertise, both in terms of treating the rare disease and in terms of the population and intervention to which the evidence is to be transferred. The involvement of external experts will therefore generally be more important in assessing the relationship between the VoS and the quality of treatment outcomes in rare diseases than in projects on more common diseases/interventions with a more informative body of evidence.

There is currently no established method for transferring evidence in studies on the relationship between the VoS and the quality of treatment outcomes. In this rapid report, a list of criteria for assessing the transferability of evidence was developed specifically for questions concerning the relationship between the VoS and the quality of treatment outcomes in rare diseases. This was based on documents on the transferability of evidence in other contexts.

Rare diseases

Developments in the diagnosis and treatment of rare diseases are currently very dynamic at both the national and European level. Examples of this include efforts to centralize the healthcare of patients with rare diseases and the establishment of registries to collect data on patients with rare diseases.

Centralization in the healthcare of patients with rare diseases

With the aim of improving the health situation of every individual with a rare disease, the National Action Alliance for People with Rare Diseases (NAMSE) was founded in 2010 in Germany. On the recommendation of NAMSE, a cross-sector healthcare concept for people with rare diseases was introduced. Cross-disease reference centres (Type A centres) were established to coordinate at least five integrated specialist centres (Type B centres). These specialist centres are registered in the Healthcare Atlas for People with Rare Diseases (SE-ATLAS) with their specific expertise [9]. According to NAMSE's National Action Plan, the implementation of this centre model is intended to promote the local, national, and international exchange of information on the current state of knowledge regarding the diagnosis and treatment of rare diseases [36]. The G-BA regulations specifying the special tasks of centres and their main focus in accordance with §136c (5) SGB V (centre regulations) came into force on 1 January 2020, setting out the quality requirements (structural, staff, and technical) as well as the special tasks of the centres for rare diseases [37]. The minimum case numbers for centres for rare diseases specified in the G-BA's quality requirements generally refer to the number of inpatients treated per year with a primary diagnosis of a rare disease and the number of interdisciplinary case conferences held. The introduction of a minimum volume regulation for specific interventions for rare diseases could result in additional centralization. Since November 2021, Type A centres can be certified by an independent agency [38].

Furthermore, in 2017, 24 European Reference Networks (ERNs) were established at the European level for people with rare and complex diseases of low prevalence. In these virtual networks, highly specialized European hospitals and reference centres work together and facilitate the exchange of the latest findings and experiences among participating hospitals, researchers, and patient groups. Individual cases can be discussed online, diagnoses made, and treatment options discussed. In addition, the ERNs coordinate and support training and continuing education measures and develop clinical practice guidelines [39]. To become a member of an ERN, the Ministry of Health at the national level must confirm the hospital's expertise in treating the specific group of rare or complex diseases covered by the ERN [40]. Consequently, European cooperation in the diagnosis and treatment of rare diseases is also linked to the establishment of highly specialized centres.

In an ad-hoc recommendation issued in 2018, the German Ethics Council pointed out that, due to the low number of cases, health care in specialized centres and by specially qualified staff is of great importance for patients with rare diseases. The minimum number of cases required for quality in health care can only be achieved for rare diseases with specialized centres or outpatient clinics [41].

Registries

Disease registries are an important option for rare diseases in order to achieve sufficiently high case numbers [42].

With the aim of recording as many people with rare diseases as possible, the epidemiological National Registry for Rare Diseases (NARSE) has been under development in Germany since 2024 [43]. This registry systematically records people with rare diseases on the basis of European standards, enabling the sharing of data at the European and international level. Treating doctors enter data into the registry based on patient consent. Registered patients can be contacted quickly and efficiently for the purpose of conducting studies [44].

The G-BA's centre regulations stipulate that specialist centres for rare diseases must report data on patients with one or more rare diseases treated at the centre to a recognized national or international disease- or disease group-specific registry via their reference centre or directly. In this respect, it is to be expected that the body of evidence for people with rare diseases will improve in the future and that, for example, scientifically sound conclusions can then be drawn about the prevalence of certain rare diseases.

7 Conclusion

This rapid report presents the development of a method to assess the relationship between the VoS and the quality of treatment outcomes for healthcare services used to treat rare diseases. The first step is always comprehensive information retrieval of studies on the given question. If no sufficiently informative studies are identified, a transfer from another population or intervention can be considered. To this end, it must be examined from which population and/or intervention this is reasonably possible.

Clinical and procedural considerations specific to the respective question are decisive when assessing transferability. A list of criteria was developed based on criteria for the transferability of evidence in other contexts. This list is intended to serve as a basis for weighing up differences between populations and interventions and for assessing transferability. This should generally be done with the involvement of clinical experts.

Once a population or intervention has been identified for the transfer of evidence, the relationship between the VoS and the quality of treatment outcomes can be examined for this population or intervention in accordance with the methods used in previous rapid reports with a sufficient body of evidence on the relationship between the VoS and the quality of treatment outcomes.

The method was developed based on literature concerning the transfer of evidence. No relevant documents containing methodological derivations of minimum volume requirements for rare diseases or requirements for hospital certification to treat specific rare diseases were identified. Likewise, no overarching methodological literature on minimum volumes for rare diseases was identified.

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The original German report is published under
https://www.iqwig.de/projekte/v24-07.html

Appendix A List of included criteria for assessment of transferability

Table 3: Criteria related to the clinical picture

Criteria[a]	Category[a]	Document
Patient types and conditions	Patients and populations	Baxter 2019
Similarity of the course of the disease	-	Dumortier 2021
Section 3.1: Disease definition: What are the manifestations or diagnostic criteria that define the disease?	Disease definition	EMA ICH 2025
Section 3.1: Disease definition: How similar are the manifestations between the reference and target pediatric populations?	Disease definition	EMA ICH 2025
Section 3.1: Disease definition: How are the manifestations measured?	Disease definition	EMA ICH 2025
Section 3.1: Disease definition: Are there similar measurements used to define manifestations of the disease in the reference and target pediatric populations?	Disease definition	EMA ICH 2025
Section 3.1: Disease definition: Are there subtypes (e.g., based on severity, genetics, molecular markers, etc.) of the disease that occur in the reference or target populations?	Disease definition	EMA ICH 2025
Section 3.1: Disease definition: What are the similarities and differences in the subtypes of the disease in the reference and target population?	Disease definition	EMA ICH 2025
Section 3.1: Course of disease: What are the similarities and differences of the clinical course of the disease between the reference and target populations? Are there differences in the course of the disease based on factors such as the age of onset of the disease?	Course of disease	EMA ICH 2025
Section 3.1: Course of disease: Are there similar endpoints and/or biomarkers available that help to measure progression of disease in both the reference and target populations?	Course of disease	EMA ICH 2025
Section 5.1.3: Factors that could limit extrapolation: Maturation and growth factors related to disease pathogenesis, disease progression, and pathophysiological, histopathological, and pathobiological characteristics can affect paediatric patients.	-	EMA 2018
Table 5: Characteristics of illness (description of conditions and comorbidities, other risk for adverse effect)	Population	Munthe-Kaas 2019
Aetiologies of disease	Population	Weise 2020
a. Extracted from the respective document.		

Table 4: Criteria related to sociodemographic patient characteristics (multipage table)

Criteria[a]	**Category**[a]	**Document**
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Large differences between demographics of study population and community patients	Population	Atkins 2011
Levels of deprivation	Patients and populations	Baxter 2019
Socio-economic diversity	Patients and populations	Baxter 2019
Rural versus urban populations	Patients and populations	Baxter 2019
Population density	Patients and populations	Baxter 2019
Level of health needs	Patients and populations	Baxter 2019
Geographical proximity of organisations	Features of organisation	Baxter 2019
Breadth of reach	Features of the initiatives / interventions	Baxter 2019
Table 2: Questions for assessing external validity (EV): To what extent do the inclusion and exclusion criteria (where relevant, other selection criteria) define the "everyday or target population" of the intervention?	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Age	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Gender	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Further socio-demographic characteristics	Study population	Bornhöft 2006
Table 1 Strategy to assess the external validity and applicability of clinical trials: (ii) Temporal, ethnical, socio-economic and geographical aspects: Ethnical Aspects - Ethnicity may interact with treatment effect.	-	Dekkers 2010
Table 1 Strategy to assess the external validity and applicability of clinical trials: (ii) Temporal, ethnical, socio-economic and geographical aspects: Geographical and socio-economic aspects - Geographical and socio-economic differences between study population and target population may affect treatment effects.	-	Dekkers 2010
Table 1 Strategy to assess the external validity and applicability of clinical trials: (iii) External validity beyond eligibility criteria: Age - RCTs mostly use strict age criteria. Generalizability beyond age criteria should be based on prior knowledge and biological plausibility.	-	Dekkers 2010

Table 4: Criteria related to sociodemographic patient characteristics (multipage table)

Criteria[a]	**Category**[a]	**Document**
Section 3.3.1: Pathophysiology of disease: Evaluation of the pathophysiology and etiology of the disease between the reference and target populations should be conducted. Collection of relevant information may include biochemical, genetic/epigenetic, cellular, tissue, organ system, and epidemiologic information that describes similarities and differences between the reference and target populations. Evaluation can also include a determination about whether differences in the clinical presentation of disease may depend upon the age of onset, age-dependent phenotypic expression, or other age-related differences. Evaluation of biomarkers that are common in the pathophysiology of the disease, including disease progression, if available, are often helpful in establishing similarities in a disease between the reference and target pediatric populations. Similarities in the outcome of untreated disease should also be evaluated.	Similarity of the disease	EMA ICH 2025
Section 3.2 Drug pharmacology: Evaluation of the drug pharmacology for the purposes of pediatric extrapolation includes absorption, distribution, metabolism, and excretion (ADME) properties, pharmacodynamics (PD) (see Section 3.3) and the mechanism of action (MOA) of the study drug. Consideration should be given to the potential influence of intrinsic and extrinsic factors on ADME such as weight, body surface area, age, organ maturation, concomitant medications, and other relevant factors (e.g., protein binding, metabolic enzymes, transporters, renal function, or choice of dosage form). [...] When evaluating the PD and MOA of a drug, considerations should be given to the potential impact of maturation-related differences, for example, in expression level and sensitivity of the drug target(s) and when applicable, potential downstream effectors.	Drug (Pharmacology) Similarity	EMA ICH 2025
Section 5.1.1: All relevant data should be thoroughly reviewed to identify potential differences between characteristics of the source and target populations e.g. body size (body mass index (BMI) or body surface), age and maturation, pre-treatment condition (e.g. immune status for vaccines) and their relationships to drug exposure (PK), pharmacodynamic response (PD) and clinical efficacy or safety.	-	EMA 2018
Does the population described for eligibility match the population to which it is targeted in the target setting?	Safety domain questions	EUnetHTA 2011
Are there any reasons to expect differences in complication rates (e.g. epidemiology, genetic issues, healthcare system (quality of care, surveillance))?	Safety domain questions	EUnetHTA 2011
Are there any differences in the following parameters? X. Demographic context	Economic evaluation questions	EUnetHTA 2011
Table 5: Participant characteristics	Population	Munthe-Kaas 2019
Chapter 5.3.3: differences in culture or lifestyle between populations	-	SIGN 2019
Demographics	Population	Weise 2020

Table 4: Criteria related to sociodemographic patient characteristics (multipage table)

Criteria[a]	**Category**[a]	**Document**
Socio-demographic status	Population	Weise 2020
Socio-economic status	Population	Weise 2020
Characteristics of the population: Cultural and linguistic diversity, Socioeconomic position, Rural / urban setting	Setting / context	Weise 2020
a. Extracted from the respective document. ADME: adsorption, distribution, metabolism and excretion; MOA: mechanism of action; PD: pharmacodynamics; RCT: randomized controlled trial		

Table 5: Criteria related to disease-specific patient characteristics (multipage table)

Criteria[a]	**Category**[a]	**Document**
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Narrow or unrepresentative severity, stage of illness, or comorbidities	Population	Atkins 2011
Level of severity of conditions	Patients and populations	Baxter 2019
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Severity of the illness	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Duration of illness	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): To what extent do the inclusion and exclusion criteria (where relevant, other selection criteria) define the "everyday or target population" of the intervention?	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Further prognostic or therapy relevant parameters?	Study population	Bornhöft 2006
Section 3.1: Course of disease: Are there similar endpoints and/or biomarkers available that help to measure progression of disease in both the reference and target populations?	Course of disease	EMA ICH 2025
Section 3.2 Drug pharmacology: Evaluation of the drug pharmacology for the purposes of pediatric extrapolation includes absorption, distribution, metabolism, and excretion (ADME) properties, pharmacodynamics (PD) (see Section 3.3) and the mechanism of action (MOA) of the study drug. Consideration should be given to the potential influence of intrinsic and extrinsic factors on ADME such as weight, body surface area, age, organ maturation, concomitant medications, and other relevant factors (e.g., protein binding, metabolic enzymes, transporters, renal function, or choice of dosage form). [...] When evaluating the PD and MOA of a drug, considerations should be given to the potential impact of maturation-related differences, for example, in expression level and sensitivity of the drug target(s) and when applicable, potential downstream effectors.	Drug (Pharmacology) Similarity	EMA ICH 2025

Table 5: Criteria related to disease-specific patient characteristics (multipage table)

Criteria[a]	**Category**[a]	**Document**
Section 3.3.1: Pathophysiology of disease: Evaluation of the pathophysiology and etiology of the disease between the reference and target populations should be conducted. Collection of relevant information may include biochemical, genetic/epigenetic, cellular, tissue, organ system, and epidemiologic information that describes similarities and differences between the reference and target populations. Evaluation can also include a determination about whether differences in the clinical presentation of disease may depend upon the age of onset, age-dependent phenotypic expression, or other age-related differences. Evaluation of biomarkers that are common in the pathophysiology of the disease, including disease progression, if available, are often helpful in establishing similarities in a disease between the reference and target pediatric populations. Similarities in the outcome of untreated disease should also be evaluated.	Similarity of the disease	EMA ICH 2025
Does the population described for eligibility match the population to which it is targeted in the target setting?	Safety domain questions	EUnetHTA 2011
Are there any reasons to expect differences in complication rates (e.g. epidemiology, genetic issues, healthcare system (quality of care, surveillance))?	Safety domain questions	EUnetHTA 2011
Would you expect the baseline risk of patients within your own setting to be the same as the baseline risk of those patients considered within the HTA report for adaptation? (assuming that patients receive the same treatment and same comparator)	Effectiveness questions	EUnetHTA 2011
Are there any differences in the following parameters? VIII. Epidemiological context (including genetic variants)	Economic evaluation questions	EUnetHTA 2011
Section 5.3.3: differences in genetic makeup of the population	-	SIGN 2019
Severity / stage of illness	Population	Weise 2020
Risk factors	Population	Weise 2020
Genetic makeup	Population	Weise 2020
Biological factors	Population	Weise 2020
Clinical parameters	Population	Weise 2020
Specialty population	Setting / context	Weise 2020
a. Extracted from the respective document. ADME: adsorption, distribution, metabolism and excretion; MOA: mechanism of action; PD: pharmacodynamics		

Table 6: Criteria related to making the diagnosis

Criteria[a]	Category[a]	Document
Table 2: Questions for assessing external validity (EV): Does the applied diagnostic procedure reflect everyday conditions and the everyday possibilities (access, necessity) respectively?	Study population	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Are the diagnostic procedures and evaluations performed by persons with similar qualification and experience as in everyday practice?	Study population	Bornhöft 2006
Checklist 1a, Section F: Are there any differences in terms of defining indications? (original text: “Bestehen Unterschiede hinsichtlich der Indikationsstellung?”)	-	Ekkernkamp 2003
a. Extracted from the respective document.		

Table 7: Criteria related to comorbidities

Criteria[a]	Category[a]	Document
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Accompanying illnesses	Study population	Bornhöft 2006
Table 1 Strategy to assess the external validity and applicability of clinical trials: (iii) External validity beyond eligibility criteria: Co-morbidities - RCTs often exclude patients with co-morbidity. Generalizability to patients with co-morbidities should only be done with caution, and can only be based on external evidence.	-	Dekkers 2010
Table 5: Characteristics of illness (description of conditions and comorbidities, other risk for adverse effect)	Population	Munthe-Kaas 2019
Key Questions KQ03 A 3: Do the studies report on any comorbidities relevant to the target population?	-	SIGN 2019
Comorbidities	Population	Weise 2020
a. Extracted from the respective document. RCT: randomized controlled trial		

Table 8: Criteria related to the intervention

Criteria[a]	**Category**[a]	**Document**
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Intensity and delivery of behavioral interventions that may not be feasible for routine use	Intervention	Atkins 2011
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Older versions of an intervention no longer in common use	Intervention	Atkins 2011
Standard of existing care	Types of services	Baxter 2019
Complexity of initiatives	Features of the initiatives / interventions	Baxter 2019
Longevity of the initiative	Features of the initiatives / interventions	Baxter 2019
Table 2: Questions for assessing external validity (EV): Does the preparation (medication, other medicinal products, other kind of interventions) reflect the usual treatment?	Intervention und control	Bornhöft 2006
Is there any consideration of when and how technical characteristics affect outcomes?	Technology's use domain	EUnetHTA 2011
Table 5: How long the intervention was implemented? (duration)	Intervention – Intervention delivery	Munthe-Kaas 2019
Table 5: What materials / manuals were used to deliver the intervention?	Intervention – Intervention delivery	Munthe-Kaas 2019
Table 5: Temporal context (e.g., if the intervention has changed over time)	Environmental context	Munthe-Kaas 2019
Intervention performance: How the intervention is delivered (eg, everyday conditions vs study conditions, visit frequency not used in typical practice).	Intervention	Weise 2020
Treatment regimen: eg, dose, schedule, duration of intervention	Intervention	Weise 2020
Relevance for current practice	Intervention	Weise 2020
Treatment trends	Outcomes	Weise 2020
Standards of care	Setting / context	Weise 2020
a. Extracted from the respective document.		

Table 9: Criteria related to the implementation of the intervention (multipage table)

Criteria[a]	**Category**[a]	**Document**
Table 2: Questions for assessing external validity (EV): Does the type of administration reflect the usual treatment?	Intervention und control	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the intervention duration reflect the usual treatment duration?	Intervention und control	Bornhöft 2006
Checklist 1a, Section F: Are there any differences in the level of technological development? (original text: “Bestehen Unterschiede hinsichtlich des Entwicklungsstandes der Technologie?”)	-	Ekkernkamp 2003
Section 3.3: Factors to consider in the evaluation of similarity of response to treatment: Assessment of similarity of response to treatment between a reference and target population should include a review of the relevant data on dose/exposure and response to treatment. The potential effect of developmental and maturational changes on the dose/exposure and clinical response should be a part of this evaluation. An understanding of the drug target and its role in normal development, disease pathology and expected response to treatment should be evaluated. For example, if a receptor does not exist in the first 6 months of life, no response to treatment would be expected for a drug only targeting this receptor in this age group. Factors that impact response that may differ between the reference and target populations (e.g., prior treatments, concomitant medications, comorbid disease, organ function, genetic makeup) should be evaluated to assess whether there is an impact on the extent to which pediatric extrapolation can be applied. In addition, understanding of the similarities and differences in the endpoints used to measure response can affect the overall assessment of similarity of response to treatment.	Similarity of Response to Treatment	EMA ICH 2025
Section 3.4.1: How does the expected treatment duration and treatment effect size in the reference population compare with the target pediatric population?	Safety	EMA ICH 2025
Are there any differences in the use of this technology within the target setting (compared to the uses described in the HTA report for adaptation)?	Technology’s use domain	EUnetHTA 2011
Are the requirements for its use (special measures needed for use/implementation, maintenance etc.) available in the target setting?	Safety domain questions	EUnetHTA 2011
Table 5: Intervention delivery details (generally)	Intervention – Intervention delivery	Munthe-Kaas 2019
Chapter 5.3.3: differences in how the intervention(s) studied is/are administered to patients in Scotland	-	SIGN 2019
Intervention performance: How the intervention is delivered (eg, everyday conditions vs study conditions, visit frequency not used in typical practice).	Intervention	Weise 2020
Treatment regimen: eg, dose, schedule, duration of intervention	Intervention	Weise 2020

Table 9: Criteria related to the implementation of the intervention (multipage table)

Criteria[a]	**Category**[a]	**Document**
Mechanics of intervention and implementation process	Intervention	Weise 2020
Feasibility of intervention in real life settings	Intervention	Weise 2020
Available technologies	Setting/context	Weise 2020
Everyday practice	Setting/context	Weise 2020
a. Extracted from the respective document.		

Table 10: Criteria related to follow-up

Criteria[a]	**Category**[a]	**Document**
Table 2: Questions for assessing external validity (EV): Does the doctor/therapist-patient relationship reflect the everyday conditions (e.g. frequency of contact, constant contact person)?	Study design and Setting	Bornhöft 2006
Are there any differences in the following parameters? XIII. Pre- and post-intervention care	Economic evaluation questions	EUnetHTA 2011
Table 5: Details of follow-up period	Outcomes	Munthe-Kaas 2019
Adherence	Intervention	Weise 2020
Length of follow up	Outcomes	Weise 2020
a. Extracted from the respective document.		

Table 11: Criteria related to concomitant treatments (multipage table)

Criteria[a]	**Category**[a]	**Document**
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Cointerventions that are likely to modify effectiveness of therapy	Intervention	Atkins 2011
Table 2: Questions for assessing external validity (EV): Does the preparation (medication, other medicinal products, other kind of interventions) reflect the usual treatment?	Intervention und control	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Are the permitted accompanying treatments the usual accompanying treatments?	Intervention und control	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Accompanying medication	Study population	Bornhöft 2006
Section 3.1: Course of disease: What are the available treatments being used for both reference and target populations?	Course of disease	EMA ICH 2025
Section 3.2 Drug pharmacology: Evaluation of the drug pharmacology for the purposes of pediatric extrapolation includes absorption, distribution, metabolism, and excretion (ADME) properties, pharmacodynamics (PD) (see Section 3.3) and the mechanism of action (MOA) of the study drug. Consideration should be given to the potential influence of intrinsic and extrinsic factors on ADME such as weight, body surface area, age, organ maturation, concomitant medications, and other relevant factors (e.g., protein binding, metabolic enzymes, transporters, renal function, or choice of dosage form). [...] When evaluating the PD and MOA of a drug, considerations should be given to the potential impact of maturation-related differences, for example, in expression level and sensitivity of the drug target(s) and when applicable, potential downstream effectors.	Drug (Pharmacology) Similarity	EMA ICH 2025
Section 3.4.1: Are there other differences between the reference and target population that could limit the extrapolation of safety (e.g., a background therapy used in a target population that may potentiate a safety signal but is not used in the reference population)?	Safety	EMA ICH 2025
Are there any differences in the following parameters? XIII. Pre- and post-intervention care	Economic evaluation questions	EUnetHTA 2011
Table 5: Participants' exposure to other interventions or previous exposure to current intervention	Population	Munthe-Kaas 2019
Table 5: Co-interventions offered to/necessary for participants	Environmental context	Munthe-Kaas 2019
Co-interventions	Intervention	Weise 2020

Table 11: Criteria related to concomitant treatments (multipage table)

Criteria[a]	Category[a]	Document
a. Extracted from the respective document. ADME: adsorption, distribution, metabolism and excretion; MOA: mechanism of action; PD: pharmacodynamics;		

Table 12: Criteria related to endpoints (multipage table)

Criteria[a]	Category[a]	Document
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Monitoring practices or visit frequency not used in typical practice	Intervention	Atkins 2011
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Event rates much higher or lower than observed in population-based studies	Population	Atkins 2011
Table 2: Questions for assessing external validity (EV): Are the tests and evaluations performed by persons with similar qualifications and experience as in every day practice?	Outcome measurements, results and evaluation	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study population reflect the everyday population in terms of: Symptoms of side effects of the interventions	Study population	Bornhöft 2006
Similarity of the response to the intervention	-	Dumortier 2021
Chapter 3.1: Course of disease: Are the short-term or long-term outcomes of the disease similar for the reference and target pediatric populations and can these outcomes be measured similarly?	Course of disease	EMA ICH 2025

Table 12: Criteria related to endpoints (multipage table)

Criteria[a]	Category[a]	Document
Chapter 3.3: Factors to consider in the evaluation of similarity of response to treatment: When evaluating the similarity of response, the following questions should be considered: ▪ Is there a similar measurement of the endpoint (e.g., clinical, biomarker, composite, etc.) used in both the reference and target populations? ▪ If the response endpoint or measurement of the endpoint is different in the reference and target populations, what is the relationship between the endpoints (e.g., clinical endpoint in the reference population in relation to a biomarker endpoint in the target population)? ▪ Are there factors (e.g., baseline severity of disease, prior treatments) that can affect both the exposure and the response? When evaluating similarity of response to treatment, consideration should be given as to whether there are age/maturity-related factors (see sections 3.1 and 3.2) that could result in differences in the measured response between the target and reference populations. For many pediatric drug development programs, the primary endpoint(s) in the target pediatric population is/are different from that in the reference population. When this is the case, a comparison of one or more components of the primary endpoint(s) and/or secondary/exploratory endpoint(s) can be used to understand the relationship between the different endpoints. For example, if there is a biomarker that is correlated with an established clinical efficacy endpoint in a reference population, and if this biomarker is also correlated with clinical efficacy in a target pediatric population, such a “bridging biomarker” could support similarity of response to treatment (see sections 4.1.5 and 4.1.6).	Similarity of Response to Treatment	EMA ICH 2025
Chapter 3.4.1: Are there other differences between the reference and target population that could limit the extrapolation of safety (e.g., a background therapy used in a target population that may potentiate a safety signal but is not used in the reference population, excipients in the formulation for the reference population)?	Safety	EMA ICH 2025
Chapter 5.1.3: Factors that could limit extrapolation: Important clinical outcomes (and hence endpoints) differ between source and target populations, increasing the complexity to set expectations, make predictions or integrate available clinical data.	-	EMA 2018
Chapter 5.1.3: Factor that could limit extrapolation: Safety information from a source population (e.g.: other paediatric population for another disease or from other drugs with the same of mode of action) may be used to predict short-term risks related to the mode of action of the drug and related to dose. However, considering that long-term risks related to growth and maturation cannot be extrapolated from adults, generation of new safety data are needed in the target population to address unexpected (age-specific) risks, thus to rely only on extrapolation for understanding of safety will not usually be possible, certainly for treatments intended to be dosed chronically.	-	EMA 2018

Table 12: Criteria related to endpoints (multipage table)

Criteria[a]	**Category**[a]	**Document**
Chapter 2.7.4: Were patient-relevant outcomes (health outcomes) examined? (original text: “Wurden patientenrelevante Outcomes (health outcomes) untersucht?”)	-	Ludwig Boltzmann Institut 2007
Table 5: Characteristics of illness (description of conditions and comorbidities, other risk for adverse effect)	Population	Munthe-Kaas 2019
Table 5: Key outcomes are considered, including those that are important to the client / patient	Outcomes	Munthe-Kaas 2019
Table 5: Adverse effects are considered	Outcomes	Munthe-Kaas 2019
Table 5: How are outcomes measured	Outcomes	Munthe-Kaas 2019
Chapter 5.3.3: different outcomes measured in studies to those that the guideline development group see as being of critical importance	-	SIGN 2019
Chapter 5.3.3: variations in baseline risk	-	SIGN 2019
Event rates	Population	Weise 2020
Definition of outcomes	Outcomes	Weise 2020
Length of follow up	Outcomes	Weise 2020
Side effects	Safety	Weise 2020
Evaluation of adverse events	Safety	Weise 2020
Factors that may contribute to the occurrence of adverse events: Patient characteristics, Type of disease, Severity of disease, Comorbidities, Clinical setting	Safety	Weise 2020
a. Extracted from the respective document.		

Table 13: Criteria related to specialization and experience of treating staff

Criteria[a]	**Category**[a]	**Document**
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Highly selected intervention team or level of training/proficiency not widely available	Intervention	Atkins 2011
Features of the workforce	Types of services	Baxter 2019
Specialist staff	Types of services	Baxter 2019
Professions involved	Types of services	Baxter 2019
Size of staff group	Types of services	Baxter 2019
Staff training	Types of services	Baxter 2019
Table 2: Questions for assessing external validity (EV): Are the interventions carried out by therapists with similar qualifications and experience as in everyday practice?	Intervention und control	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Are the investigators the regular contact persons (e.g. GP or relevant clinic doctor, or are they at least comparable in terms of training, status, experience, preferences; does the number of contact people reflect the usual setting)?	Study design and Setting	Bornhöft 2006
Table 1 Strategy to assess the external validity and applicability of clinical trials: (iv) Applicability of study results: Treating physician - Treatment effects can depend on skills of treating physicians.	Setting	Dekkers 2010
Is the necessary expertise (knowledge and skills) available in the target setting?	Safety domain questions	EUnetHTA 2011
a) Is safety particularly dependent on training? b) Are there types of teams to which the procedure should be limited for safety reasons? c) Is there a need for special training or certification to deliver the intervention properly. d) Would it be possible (affordable) to organise such training, if any?	Safety domain questions	EUnetHTA 2011
Are there any differences in the following parameters? VII. Personnel characteristics	Economic evaluation questions	EUnetHTA 2011
Table 5: Skills of service providers	Service providers (individuals)	Munthe-Kaas 2019
Table 5: Training of service providers	Service providers (individuals)	Munthe-Kaas 2019
a. Extracted from the respective document.		

Table 14: Criteria related to the setting (multipage table)

Criteria[a]	**Category**[a]	**Document**
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Standards of care differ markedly from setting of interest	Setting	Atkins 2011
Table 1. Characteristics of individual studies that may affect applicability: Condition that may limit applicability: Specialty population or level of care differs from that seen in community	Setting	Atkins 2011
Number and type of organisations	Features of organisation	Baxter 2019
Particular elements of infrastructure or services	Features of organisation	Baxter 2019
Table 2: Questions for assessing external validity (EV): Does the study situation reflect the common treatment situation?	Intervention und control	Bornhöft 2006
Table 2: Questions for assessing external validity (EV): Does the study setting reflect the everyday conditions?	Study design and Setting	Bornhöft 2006
Section C, 10.: Can the results be applied to the local population? HINT: Consider whether your local setting is likely to differ much from that of the study.	-	CASP 2018
Table 1 Strategy to assess the external validity and applicability of clinical trials: (iv) Applicability of study results: Treatment setting - The setting of the treatment, i.e. the use of a study nurse, the frequency of controls and the availability of diagnostic procedures, may influence treatment results.	Setting	Dekkers 2010
Checklist 1a, Section F: Are there any differences in terms of health care contexts, conditions and processes? (original text: “Bestehen Unterschiede hinsichtlich der Versorgungskontexte, -bedingungen, -prozesse?”)	-	Ekkernkamp 2003
Checklist 1a, Section F: Are there any differences in remuneration systems? (original text: “Bestehen Unterschiede hinsichtlich der Vergütungssysteme?”)	-	Ekkernkamp 2003
Are there any differences in the following parameters? III. Relative costs	Economic evaluation questions	EUnetHTA 2011
Are there any differences in the following parameters? IV. Indirect costs	Economic evaluation questions	EUnetHTA 2011
Are there any differences in the following parameters? VI. Technological context	Economic evaluation questions	EUnetHTA 2011
Are there any differences in the following parameters? XIV. Integration of technology in health care system	Economic evaluation questions	EUnetHTA 2011

Table 14: Criteria related to the setting (multipage table)

Criteria[a]	**Category**[a]	**Document**
Section 2.2: There may be important differences in implementation across settings that can weaken inferences regarding applicability	Intervention	Guyatt 2011
Table 5: In which settings was the intervention delivered? (physical setting, etc.)	Intervention – Intervention delivery	Munthe-Kaas 2019
Table 5: Type of service provider	Service providers (individuals)	Munthe-Kaas 2019
Table 5: Service provider characteristics	Service providers (individuals)	Munthe-Kaas 2019
Table 5: Size and structure of the implementing organization	Implementing organisation	Munthe-Kaas 2019
Table 5: Implementing organization level or specialty of care	Implementing organisation	Munthe-Kaas 2019
Table 5: Systems context (Health systems arrangements)	Environmental context	Munthe-Kaas 2019
Table 5: Physical or geographic setting	Environmental context	Munthe-Kaas 2019
Section 5.3.3: differences in how care is delivered, or availability of technologies or resources	-	SIGN 2019
Care pathways	Setting/context	Weise 2020
Level of care	Setting/context	Weise 2020
Primary, secondary, tertiary care	Setting/context	Weise 2020
Fee or payment structure	Setting/context	Weise 2020
Insurance system	Setting/context	Weise 2020
Implementation of PHI (Public Health Interventions) in a specific setting: Responsibilities, Implementation barriers, Provider skills, Resource availability	Setting/context	Weise 2020
a. Extracted from the respective document.		