Evidence generation throughout paediatric medicines life cycle

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REVIEW ARTICLE

Evidence generation throughout paediatric medicines life cycle: findings from collaborative work between European Medicines Agency (EMA) and EUnetHTA on use of extrapolation

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Abstract

Drug development for children presents unique challenges and is highly regulated. Novel approaches, such as the use of extrapolation to address, for example, the need to avoid unethical studies, whilst supporting robust evidence generation have been developed in support of benefit/risk considerations by regulatory authorities. This is only one step in the decision-making process towards access, which in Europe also includes health technology assessment (HTA) bodies.

Discussions related to evidentiary requirements in small populations using scientific evidence transfer have been identified as a priority action by European Medicines Agency/European Network for Health Technology Assessment 21 (EMA/EUnetHTA 21). We describe the outcome of this work and reflect on the discussions that had taken place on how to leverage prior knowledge through identifying and addressing uncertainties during life cycle management to support regulatory and HTA decision-making. Using examples, we explore the range of applications for evidence generation and offer regulatory and HTA insights on key design considerations for

Abbreviations: EMA, European Medicines Agency; EUnetHTA, European Network for Health Technology Assessment; EU, European Union; HTA, Health technology assessment; HTAb, Health technology assessment bodies; HTAR, Health technology assessment regulation.

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producing better evidence, reflecting our shared ambition. Early interactions with all respective stakeholders, particularly between regulators and HTA bodies are key to optimise data generation and utility in children.

In Europe, the HTA regulation will offer opportunities for collaborations, which are important for all development efforts. We collaboratively explored the unique specific challenges relating to paediatric drug development, ethically and in its ability to leverage prior knowledge, as exemplified using extrapolation. Learnings from these offer opportunities to further develop methodology on how to leverage uncertainties across a product's life cycle for small populations generally.

KEYWORDS

extrapolation, benefit/risk decision making, health technology assessments, paediatrics

1 | BACKGROUND

Drug development is highly regulated so that a medicine is of good quality, safe and efficacious. In the European Union (EU), the legal framework sets out rules and responsibilities for the authorisation of medicines, and it is the responsibility of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to assess a product's benefit–risk balance. Additional legal frameworks are in place to further foster medicines development in areas of unmet medical needs, such as in children. This is the background to the EU Paediatric Regulation that governs regulatory decision-making on mandatory paediatric investigation plans (PIPs) agreed by EMA's Paediatric Committee (PDCO) (Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, 2004). Its objective is to stimulate timely development of novel medicines for children based on ethical and high-quality research.

Research involving children presents unique challenges. One of the most significant challenges is that it is ethically imperative to avoid the unnecessary enrolment of children in clinical trials, as highlighted by the Paediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, 2004). Novel approaches such as extrapolation allow to address this challenge. Extrapolation relies on using prior knowledge, for example from adults to support the benefit–risk assessment in paediatric patients. Based on that, an extrapolation framework has been developed internationally by regulators under the guidance from the International Council for Harmonisation (ICH) (European Medicines Agency (EMA), 2022; European Medicines Agency (EMA), 2024; European Medicines Agency (EMA), 2018), supporting its consistent use across regions. Methodologically, the starting point for considering whether it is acceptable to use extrapolation in drug development relies on demonstrating the similarity of the disease between reference and target population, as discussed as part of the extrapolation concept, with remaining identified uncertainties addressed within the extrapolation plan.

What is already known?

- Extrapolation to support evidence generation for paediatric medicine development is acknowledged as an important tool.

What this study adds?

- We describe the first-ever collaborative work with health technology assessment (HTA) bodies on extrapolation use.

What is the clinical significance?

- Evidence generation using extrapolation needs to be robust supporting regulatory and HTA decision-making.

The starting point for paediatric regulatory support within a paediatric investigation plans is the potential for a product to offer therapeutic benefit in areas of unmet medical need, independent of whether it is a paediatric medicines development which is 'adult led'. That is, conducted on the back of an adult development (e.g. treatment of asthma or treatment of diabetes) as is the common situation or 'paediatric led' in conditions exclusively or mainly affecting children. Once a target population is identified, evidentiary requirements are discussed making use of all available knowledge as applicable.

The use of extrapolation should be agreed prospectively and always based on scientific considerations. Extrapolation must not be a tool used to retrofit available data to support a benefit/risk assessment, because a development has become 'unfeasible or challenging to complete' over time. So, the use of extrapolation implies the need to identify evidence gaps and mitigate uncertainties at an early stage, prior to applying for marketing authorisation. Whilst for others it may

be acceptable and sometimes even only possible to address identified evidence gaps after authorisation, for example in the real-life setting, this brings challenges for regulators. During development it is important to identify what knowledge gaps need to be addressed, but also how to best ensure these uncertainties are addressed to a sufficient level of confidence in the pre-authorisation phase (particularly important in neonates with different maturational and developmental changes; European Medicines Agency [EMA], 2008).

The ambition of all stakeholders is to support paediatric development plans that ultimately generate the best evidence enabling access to new and innovative medicines. However, it is acknowledged that the use of novel approaches like extrapolation may challenge generation of data that addresses evidence needs of other decision-makers, such as Health Technology Assessment bodies (HTAb). This has been recognised and identified as a priority action for further collaboration between EMA and EUnetHTA21 (European Medicines Agency [EMA], 2022), which we are reporting on.

2 | EXTRAPOLATION AS A TOOL

It is important to ensure equal understanding of terminologies used. The use of extrapolation by medicines regulators involves two key aspects, the extrapolation concept and the development of an extrapolation plan, which guides the generation of evidence (European Medicines Agency [EMA], 2024; European Medicines Agency [EMA], 2018).

The extrapolation concept summarises the existing evidence with respect to disease, drug pharmacology and response to treatment in both the reference and the target population to identify gaps in knowledge to be filled by the extrapolation plan (European Medicines Agency [EMA], 2022). Importantly, adequate use of extrapolation in support of evidence generation is approached as a continuum of similarity/dissimilarity in a disease, rather than a binary decision (see Figure 1). If it is concluded that disease and treatment response is similar in the reference and the target population, performing a randomised controlled efficacy and safety trial in the target population would not be necessary (European Medicines Agency [EMA], 2024). In this case, the extrapolation plan mainly consists of finding doses that match plasma concentrations in adults where efficacy and safety have been established (target exposure). This is enabled by modelling and simulation (M&S) that also incorporates pharmacokinetic (PK), including supportive efficacy and safety data from a single arm trial in children.

A detailed scientific discussion on disease similarity, relevance of the pharmacological target and anticipated response to treatment is the key.

3 | EXTRAPOLATION USED TO SUPPORT EVIDENCE GENERATION IN AGREED PAEDIATRIC INVESTIGATION PLAN (PIP) DECISIONS

Supporting the detailed technical discussions between EMA and EuNetHTA21, an as-is analyses on the proposed and agreed use of extrapolation within paediatric investigation plans (PIPs) of all initial paediatric investigation plan decisions issued by EMA between 1 January 2019 and 30 April 2021 was conducted, which we are summarising in the succeeding texts.

A total of 268 paediatric investigation plan applications were considered during the observation period. Of these, 69 (26%) paediatric investigation plan applications proposed extrapolation approaches (ranging from exposure matching based on modelling and simulation alone or

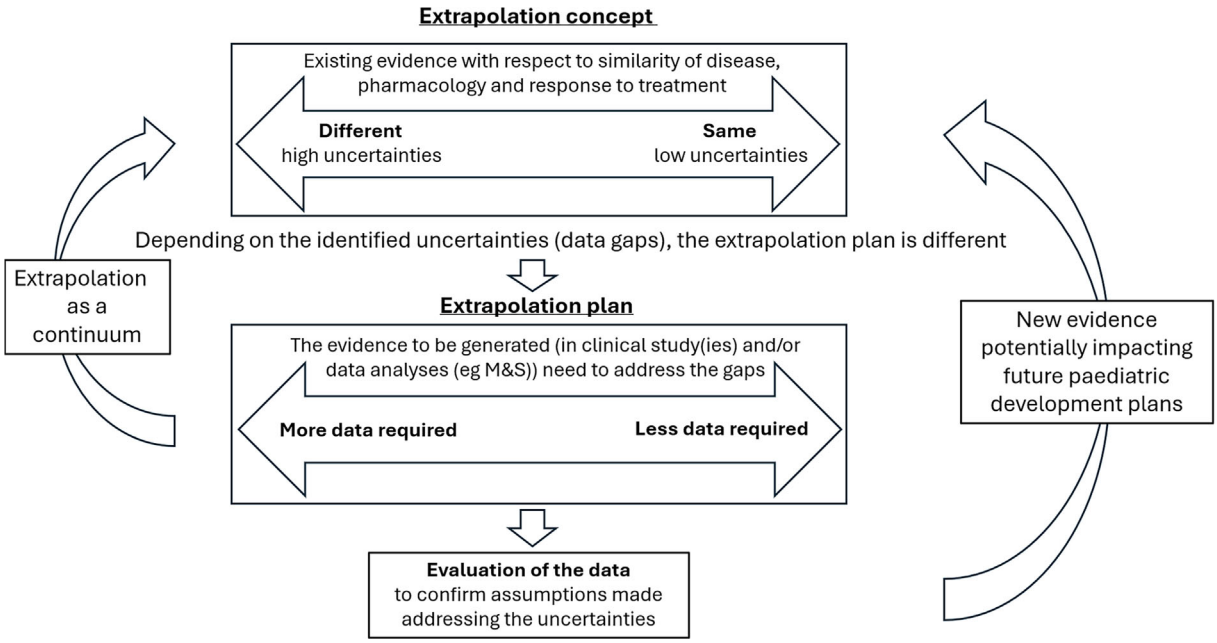

FIGURE 1 Extrapolation as a continuum and not a single time point assessment; adapted from International Council for Harmonisation (ICH) E11A guideline (European Medicines Agency (EMA), n.d.-b).

using a combination of underpowered randomised controlled trials and modelling and simulation analyses). During discussions on the extrapolation concept, Paediatric Committee disagreed with the initial proposed use of extrapolation in 5 per 69 (7%) cases, because the disease was not considered to be similar and/or because of maturational and developmental differences of the pharmacological target across populations, such as in the therapeutic area of neurology and immunology.

For the 64 remaining paediatric investigation plans, we mapped how extrapolation had been agreed to support product development across all paediatric age subsets (Figure 2) by examining individual paediatric investigation plan studies in the extrapolation plan (clinical studies and modelling and simulation analyses):

- In three (5%) cases, modelling and simulation analysis alone was considered appropriate to support the paediatric development across the targeted paediatric age groups without clinical trial data from children (scenario A).
- In only one (2%) case, extrapolation from an older paediatric age group was accepted to support development in a younger age subset, without the need for clinical trial data (this includes pharmacokinetic [PK] data) (scenario B).
- The most predominant extrapolation (66% – 42 cases) approach utilised a combination of clinical trial data supported by modelling and simulation analyses across all paediatric age groups (scenario C).
- No paediatric investigation plan agreed on a stand-alone development in an older age group, with modelling and simulation analyses only to support development of a younger age subset (scenario D).
- In 18 (28%) paediatric investigation plans, development in a younger population was supported by clinical trial and modelling and simulation data, where data generation for the older age subset relied in clinical trial data only (scenario E).

When looking into the 60 cases with agreed clinical trials included in the extrapolation plan, 39 (65%) included randomised controlled and 21 (35%) single-arm trials. Potential use of Bayesian statistics was discussed equally often in situations of a development supported by a randomised trial (9 per 39 cases; 23%) and single-arm trial development (5 per 21 cases; 24%).

Overall, this analysis shows that extrapolation is usually accepted when proposed to support paediatric development on scientific grounds with uncertainties mainly addressed through clinical trial data (single-arm trial and/or randomised controlled trials) and supported by modelling and simulation analyses of pharmacokinetic/pharmacodynamics data.

4 | CASE EXAMPLES—PRACTICAL CONSIDERATIONS AT TIME OF MARKETING AUTHORISATION APPLICATION

Following the paediatric development overview, the focus moved to case examples and the respective data packages in support of a paediatric indication. The following reflections on successful developments provide additional context related to how uncertainty management was approached by the Committee for Medicinal Products for Human Use.

When the same exposure is expected to provide similar response in adults and children, exposure matching can be used. It is important to ensure that the target exposure for the exposure matching exercise is defined in advance. This is usually derived from the pivotal adult studies where efficacy and safety have been established. In this regard, pre-specified adequate sampling of pharmacokinetic data is paramount in all age groups that need to be defined (European Medicines Agency [EMA], 2018).

In principle, pharmacodynamics matching follows same principles as pharmacokinetic matching but is at present less commonly used. pharmacodynamics markers used should reliably predict a clinical effect in the paediatric population and adult data on the pharmacodynamics markers alone may not be sufficient.

Model-based approach is often used to study pharmacokinetic, pharmacodynamics and their relationship. Modelling and simulation methods can also support quantitative exposure–response analyses based on clinical outcome measures such as a validated index score.

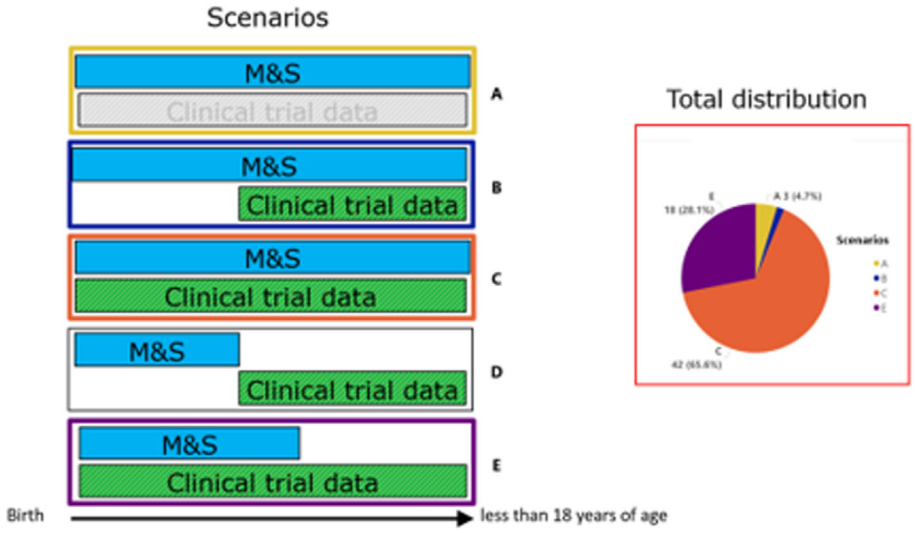

FIGURE 2 Overview of paediatric developments agreed in paediatric investigation plans (PIPs) and use of extrapolation across different age subsets (from birth to less than 18 years of age). Extrapolation plans ranging from using modelling and simulation (M&S) only for all age subsets (scenario A) to a mixture of a clinical trial data supported by M&S, complementary (scenarios C and E) or with different age subsets serving as target populations, respectively (scenarios B and D).

5 | CASE EXAMPLES

Depending on the identified remaining uncertainties, there may be situations where benefit/risk assessment can be concluded based on modelling and simulation of exposure levels only (as reflected in scenario A, Figure 2), particularly in adolescents where maturation considerations are often not an issue. Availability of adolescent pharmacokinetic data from different programmes may increase the robustness and validity of the simulation. An example of this is the treatment of malignant melanoma. Given the similarity in disease pathophysiology and response to treatment, simulated exposure to treatment in adolescent and adult patients using models with sufficient validity may be sufficient to show comparable exposure between adolescents and adults with a certain body weight (as reflected in the European Public Assessment Report [EPAR] of **relatlimab**/**nivolumab** (European Medicines Agency [EMA], 2022).

Similarly, in case of differences in exposure levels in paediatric patients compared to the intended target exposure it is important to discuss to which degree any such exposure difference is clinically relevant. This could lead to additional safety or efficacy concerns. This was discussed in the European Public Assessment Report on **emicizumab** and the observed differences (potential higher exposure in neonates and younger children) were not considered clinically relevant, leading to the inclusion of patients down to birth in the indication support by modelling only in the youngest age subset (as reflected in scenario B) (https://www.ema.europa.eu/en/documents/assessment-report/hemlibra-epar-public-assessment-report_en.pdf Accessed 5 April 2024, n.d.). To overcome or mitigate differences in exposure levels in paediatric patients, the dose may need to be adjusted to better match target exposure where efficacy and safety have been established. This can be achieved through modelling and simulation of new dosing regimens, which should preferably be confirmed with pharmacokinetic data from patients (European Medicines Agency [EMA], 2018).

Hepatitis C is a condition where extrapolation is considered appropriate because of the similar pathophysiology of the infectious disease and spectrum of activity of the antiviral agent (hepatitis C virus (HCV) viral load as pharmacodynamics target). Paediatric investigation plans have been agreed (reflective of scenario C) and indications granted, using an extrapolation strategy consisting of matching similar plasma pharmacokinetic concentrations as in adults, where efficacy and safety have been established (exposure matching example). This can be based on pharmacokinetic data from a single-arm trial in children, supported by modelling and simulation (as described in detail in the European public assessment report of **sofosbuvir**/**velpatasvir** (European Medicines Agency [EMA], 2016). The European Public Assessment Report describes the importance to ensure that the pharmacokinetic data generated in all relevant age subsets can describe pharmacokinetic parameters with high confidence supporting the exposure matching exercise. This has proven challenging in some cases, especially in the youngest age subsets, where the variability in pharmacokinetic is usually highest, requiring larger sample sizes that needs careful study planning (optimised pharmacokinetic sampling schedule and sufficient number of patients by defined age subsets as necessary).

Generation of additional controlled clinical data might be required in situations of high uncertainties, for example related to disease similarity, as shown by the paediatric investigation plan analyses presented in the therapeutic areas, such as neurology, immunology or metabolic diseases. Controlled data can also be relevant for first in class products with limited or no data available on treatment response in different age subsets. In these cases, it is important that paediatric requirements are taken into account early in the development process even for the adult studies (e.g. additional relevant endpoints that will be essential to the extrapolation approach between the adult and paediatric population). In addition, how the clinical data will be analysed and criteria for when the extrapolation will be considered successful should be pre-specified.

The case examples show successful uses of extrapolation to support regulatory decision-making in Europe. But more systematic evaluations are needed in the future, following International Council for Harmonisation E11A implementation as regards successful applications and its utility for HTA decision-making. It nonetheless shows that the regulatory acceptability of extrapolation and the necessary data to be generated, either within clinical studies or modelled by means of utilising prior knowledge, depends, case by case, on current knowledge and knowledge gaps of the product and the disease. The more uncertainty identified related to the product and its pharmacological target as well as the disease, the more additional clinical data in children may be required, including modelling and simulation to optimise paediatric development.

As mentioned, the scientific rationale behind using an extrapolation approach, the residual uncertainties deriving from such approach and subsequent data considered necessary to be generated in, for example, clinical trials, are all important elements which need to be well communicated across all relevant regulatory decision-makers and beyond, including HTAb.

6 | INTRODUCTION TO HEALTH TECHNOLOGY ASSESSMENT BODIES (HTABS)

To better understand the difference between the regulatory and HTA scope, the following general considerations related to HTA work are summarised. HTA is defined as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its life cycle (O'Rourke et al., 2020). The objective of HTA is to compare the relative effectiveness of new or existing health technologies, by focussing on the added value of a health technology in comparison with other new or existing health technologies (Regulation [EU] 2021/2282) (Regulation [EU] 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance), 2021).

Health technology assessment has not been harmonised for many years. However, this is one of the objectives of the new regulation, which entered into force in January 2022 and will be of applied in January 2025 (Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance), 2021), to establish the basis and methodology to ensure an efficient use of available resources and reinforce quality of HTA in the EU and reduce duplication of work by HTA authorities and bodies.

HTA assessments involve both clinical and non-clinical aspects of a health technology, depending on the health-care system in question. The Union's co-funded joint actions on HTA (EUnetHTA Joint Action and the later EUnetHTA 21 consortium) have identified nine domains for evaluating health technologies. Of these nine domains, four are clinical and five are non-clinical aspects. The four clinical domains of assessment involve identifying the health problem and assessing the existing health technologies, examining the technical characteristics of the health technology under assessment and assessing its relative safety and clinical effectiveness. The five non-clinical assessment domains concern cost and economic evaluation of the health technology, and its ethical, organisational, social and legal aspects. The Regulation (and its implementing acts, now in progress) focusses mainly on collaboration on the assessment of clinical domains at European level, although the Commission shall support the cooperation and the exchange of scientific information among Member States on non-clinical assessments on health technologies. In this sense, the joint work on clinical aspects will mainly focus on the Joint Clinical Assessments (JCA) reports and on the Joint Scientific Consultations (JSC). According to the regulation of HTA (HTAR), Joint Clinical Assessments involves the scientific compilation and the description of a comparative analysis of the available clinical evidence on a health technology in comparison with other health technologies or existing procedures. Meanwhile, the goal of Joint Scientific Consultations is to allow information exchange with health technology developers (HTDs) on their development plans for a given health technology, in order to facilitate the generation of evidence that would meet the requirements of a subsequent Joint Clinical Assessments. Joint Scientific Consultations can be carried out in parallel with regulators, in particular with the scientific advice on medicinal products from EMA (with the Scientific Advice Working Party) or with that for medical devices (Expert Panel). This joint work will not limit future complementary analyses by the Member States, in particular on the health technologies for which a Joint Clinical Assessments report is available. This work will ensure the highest quality of the assessment, ensure a wide acceptance and enable pooling of expertise and resources across national HTA authorities, ensuring timely results.

This HTAR, however, shall not interfere with the exclusive national competence of national pricing and reimbursement (P/R) decisions, or affect any other competences that concern Member States' management and delivery of health services, or medical care, or the allocation of resources assigned to them. This is why the focus of this technical collaborative effort focussed only on clinical evidentiary requirements.

According to the HTAR, the available evidence should answer the PICO question (a mnemonic used to describe the four elements of clinical foreground question: Population, Intervention, Comparison and Outcome). The PICO question(s) may cover the indication of the medicinal product under assessment. The assessment scope of a requested PICO within a Joint Clinical Assessments shall reflect EU Member States needs. The PICO answer then provides information on the specific data requirements. Ideally, the clinical trials and studies developed by the HTD should enable providing answers to each element of the PICO question(s). Nevertheless, HTA assessment often encounters that the available evidence only partially addresses some of the required elements of the PICO question. As a consequence, HTA reports explain the strengths as well as the gaps and limitations of the available evidence.

Therefore, clinical data of the medicinal product are generally required. These data shall preferably derive from comparative clinical trials, which are randomised, blinded and include a control group (preferably an active substance), or, alternatively, from post-authorisation comparative studies available at the time of evaluation. In this sense, in paediatrics there will be clinical developments that lack some data or that have a scarcity of data in some aspects. This is where the joint work developed in collaboration with all the stakeholders involved, because the initial stages of development will have a very relevant role. However, HTA approach should not per se exclude other evidence coming from observational studies, including those based on real-world data (RWD), when such studies are accessible and of adequate quality.

The authorisation in paediatrics ensures pharmacovigilance assessments and is hence important. This entails additional data collection and monitoring of post-authorisation data as part of life cycle management, further able to support other decisions, such as HTA-decision making. Moreover, given the high unmet need for several medical conditions in the paediatric population and the specificity of the regulatory framework, the use of extrapolation might be accepted by HTAb when appropriately and prospectively justified.

Although the scope and objectives of regulators and HTAb are different, they should be understood as complementary and equally necessary. So too are the respective evidentiary requirements to support regulatory and HTA decision-making. Nonetheless, there are general design considerations which are important to both bodies. These were explored and are described in the succeeding texts for the benefit of developers.

7 | DESIGN AND DEVELOPMENT STRATEGY ELEMENTS OF RELEVANCE—JOINT REGULATORY AND HTA REFLECTIONS

7.1 | Inclusion of considerations on controls

As described above, the need for comparative evidence generation in context of the use of extrapolation remains case and context specific to adequately addressing identified evidence gaps. It remains

important to generate data that allow contextualisation of the product under development against a control or a potential comparator. It is worth mentioning that at the level of terminology for regulators, the control group corresponds to the arm used as a basis for a comparison in a clinical trial (and can be the placebo or an active substance) and at the level of HTA, comparator will be the treatment most frequently found in clinical practice (such as Standard of Care [SoC]) and it could correspond to the control group of a comparative trial or other therapeutic alternatives used to establish the comparison in terms of effectiveness.

The choice of controls used/needed must be taken into consideration upfront and needs to be discussed as part of the extrapolation plan, such as use of an open label single-arm trial considering the methodological implications (European Medicines Agency [EMA], 2023) versus a randomised controlled study with an alpha level higher than the standard value of 0.05 (see also Section 7.3). Considerations should also cover the use of an active versus placebo control and also availability of historical control data and its fitness for purpose.

Open-label single-arm trials introduce bias in the interpretation of data, in particular, for those endpoints related to time to event (such as Progression Free Survival [PFS] and Overall Survival [OS]) and those health outcomes frequently used to measure quality of life (QoL), reported either by the patient or the clinician (Patient-Reported Outcomes [PRO] and Clinician-Reported Outcomes [ClinRO]). This kind of design should carefully select clinical meaningful endpoints whose interpretation is objective and do not depend on comparison with another arm.

The design for single-arm trials should carefully select clinical meaningful endpoints whose interpretation is objective, validated in a robust and appropriate manner, and that do not depend on the comparison with another arm. Traditionally, objective response rate (ORR) is the most frequently used primary endpoint in single-arm oncology studies, but it may not apply to certain situations or diseases, and this should be discussed upfront.

Uncontrolled trials do not allow relative effectiveness assessment. In the context of HTA, uncontrolled trials are of very limited value for estimating treatment effectiveness. In this respect, HTAb recommend incorporating an active comparator in their clinical programmes, whenever feasible and if possible, SoC. If performed at least in the adult population, then it would be easier to validate (whenever possible) an extrapolation approach for the paediatric population or a particular subpopulation and always following the regulatory approach.

In order to decide the best comparator, the EUnetHTA Joint Actions have developed guidelines for stakeholders involved in the development of medicines and, although these guidelines are written for a global population (not specifically developed for children), key points of interest can be extracted from them with considerations about the choice of the comparator (Comparators & Comparisons, 2015; Comparators & Comparisons: Direct and indirect comparisons, 2015). According to those guidelines 'under ideal circumstances', the comparator for a European-wide acceptable assessment would be the SoC according to high-quality clinical practice guidelines at European or international level, with good quality evidence on effect size and adverse effects from medical literature. However, this is not easily established for all circumstances and in all countries, that is why the joint work would be helpful in order to minimise differences among countries or even among regions.

As indicated in those guidelines, only for orphan medicines, the Orphan Medicinal Designation established a consensus position on standard of care, although in that case, the considered comparators should be medicines authorised within the European Union. Thus off-label medicines or other medicines used in other circumstances are not contemplated. However, in other minority populations, such as paediatrics, other considerations may also be established. In this respect during the evaluation of paediatric medications, it is common that clinical practice includes medicines used off-label. This also occurs, but less frequently, in the same indication in adults. Identification of appropriate comparators in paediatrics, especially when used off-label, may be challenging and will have to be supported by quality literature and expert clinicians.

Finally, historical control data could support in some instances, a HTA. The obtained data could be biased by the internal differences in baseline and demographics of patients under study (e.g. age and degree of severity could be really different among patients), as well as timepoints and period under study, endpoints and comparators available during this period. However, in paediatrics, in some circumstances, an acceptable control could be the same patient, instead of an external control group (for example by measuring the evolution of a biomarker or by making baseline comparisons) that would better reflect the comparison between medicines.

7.2 | Appropriateness of the endpoints

From a regulatory perspective, reflections on the most adequate pharmacodynamics and paediatric relevant clinical endpoints are the key. Preferably, the same endpoints should be applied across both source and target populations. However, the endpoints must be tailored to the target population and should be suitable for the specific study design. Endpoints, for example for single-arm trials, whether a biomarker or a clinical endpoint, are considered most appropriate, if it allows attributing change to the active treatment and change in observation would occur only at a negligible extent in the absence of the treatment (for example overall response rate in a single-arm trial in oncology - see also above section on considerations on controls). For biomarkers, validation with clinical data in children is necessary, as adult data alone are insufficient. This consideration is crucial in the context of what is planned to be extrapolated, such as a biomarker or a clinical endpoint. In any case, from a regulatory and HTA perspective, whether through established surrogacy and/or the use of a clinical endpoint, it must reliably indicate a clinically meaningful improvement in the target population.

Given the typically limited sample size in extrapolation studies, decisions often rely on the totality of the data. Therefore, it is

particularly crucial to select appropriate endpoints that reflect, for instance, the natural history of the disease.

Furthermore, when extrapolation is based on exposure response matching using a biomarker and/or a clinical endpoint indicative of the immediate effect of the drug, considerations regarding long-term relevance in comparison to the natural history of the disease, the maintenance of effect, or the sustainability of the described benefit beyond the data generated as part of the extrapolation exercise become essential, especially if long-term treatment is anticipated.

Pre specification of analysis is paramount as part of the extrapolation plan with a focus on how the paediatric pharmacokinetic/pharmacodynamics, exposure response and/or clinical efficacy, and safety data will be analysed and interpreted.

From an HTA perspective, EunetHTA Joint Action and EUNetHTA 21 have worked on several guidelines that aim to cover main aspects related to endpoints (Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints, 2015; Endpoints used for Relative Effectiveness Assessment Health: related quality of life and utility measures, 2015; Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints, 2015; Endpoints used for Relative Effectiveness Assessment: Composite endpoints, 2015; Endpoints used in Relative Effectiveness Assessment: Safety, 2015; EUnetHTA 21 – Individual Practical Guideline Document D4.4 – OUTCOMES (ENDPOINTS), 2023). In addition, the HTA Coordination Group (HTA CG) has already adopted the guidance on outcomes for Joint Clinical Assessments pursuant HTAR (Guidance on outcomes for joint clinical assessments, 2024), which would be used for the selection of outcomes during the scoping process and the Joint Clinical Assessments report. In this respect, 'outcome' is any concept that can be used for the estimation of relative effectiveness and safety of a health technology, such as mortality, remission, disease control, function, health-related quality of life (HRQoL) and symptoms. Because of the use of extrapolation, clinical data in children usually do not rely on clinical meaningful endpoints that measure directly the therapeutic effect (mortality, morbidity, adverse events and hospitalisation), but on pharmacokinetic and pharmacodynamics parameters, and somehow this would limit the interpretation of the data. Furthermore, it would be beneficial if the developer explores the use of secondary endpoints related to the therapeutic effect. In this respect, quality of life is a valuable and critical endpoint for HTA evaluation in order to consider the added benefit of a medicine. As different instruments give different results, HTA encourages to use validated health-related quality of life tools whenever possible. Furthermore, utility estimates for children could be different from adults and could be biased by the interpretation performed by caregivers and relatives, for this particular reason it is recommended that health-related quality of life to be assessed by the patients themselves instead by proxies. However, proxies' assessment is understandable in particular cases, such as cognitively impaired children or those with reduced capacities to communicate, as newborns or very small children, or even those with severe degrees of disease. Finally, sometimes the quality of life of caregivers may be relevant for an HTAb, considering that the caregivers who take care of those patients that are highly dependent and that require medical personalised attention to be given by them. In some instances, scores and items related to health-related quality of life may be generated after the approval of the medicine, during the post-authorisation phase or by using real-world data (see also succeeding discussion), and somehow may also support the HTA evaluation. It is worth mentioning that from an HTA perspective, not only the definition of the outcome is pertinent but also the timing and follow-up, as this could be different according to the characteristics of the disease (for chronic diseases, for example, the occurrence of fatal events in a long-term follow-up) in comparison with an acute condition where symptoms, adverse events and quality of life would be more clinically relevant. This may have an impact when considering paediatric developments. As the acceptability of an outcome is subject to Member State's interpretation and thus may differ, joint discussions between regulators and HTAb would be essential to reaching consensus, not only during a Joint Scientific Consultations but also during the scoping process of a Joint Clinical Assessments.

7.3 | Statistics

Methodological considerations include the specification and justification of the statistical analysis. Success criteria for a paediatric study are to be specified and may be different from that of a usual confirmatory study in adults. This could refer to explicitly using increased type-1 error rate or the incorporation of data from studies in adults, for example using Bayesian methods or statistical models that would allow for an extrapolation accounting for covariates that differ between adult and paediatric population. Increasing type-1 error rate of the statistical test in the paediatric population may be informed by the evidence in adults. For example, one approach has been outlined by Hlavin et al. (2016) who proposed a framework based on prior beliefs in order to investigate how the (frequentist) significance level for the test in the paediatric population can be relaxed.

In case stand-alone evidence comes from paediatric patients only, this would be considered insufficient. Then, the efficacy conclusion would be based on a synthesis of a small paediatric trial and external (adult) data, and reasonable assumptions should be made regarding the statistical model for evidence synthesis. In general, a model that would result in an averaging effect of the paediatric and the adult population could be misleading. Instead, reasonable assumptions on how to use (extrapolated) adult data should be made and justified. Because it is difficult to quantify the uncertainty of extrapolation, sensitivity analyses with modified assumptions are important to ensuring the robustness of any conclusions drawn.

The paediatric population is not homogenous, differences could be observed based on the age and on the severity of the disease according to a different pattern or manifestation of it. Differences should be described and considered at the very early drug development. If definition of subgroups is considered appropriate, whenever possible, these should be pre-specified, stratified and provided with

sufficient power and sample size for a differential analysis among them.

7.4 | Use of real-world evidence in addressing uncertainties within extrapolation

Real-world evidence (RWE) is derived from the analysis of real-world data (data that describe patient characteristics and delivery of health care in routine clinical practice) and might have the potential to provide complementary information to address uncertainties within the extrapolation concept and inform the extrapolation plan, thereby supporting the development as well as the safe and effective use of medicines in children.

In this sense, there are three main areas of paediatric extrapolation in which real-world data/real-world evidence may be useful as supportive data. It may provide additional information to inform the assessment of disease similarity between adults and the paediatric population within or across related conditions. This may be achieved by answering questions related to similarities in the modalities expressed by the patients of clinical characteristics such as disease stage or severity, the presence of comorbidities, natural history of disease and disease progression, clinical endpoints and how they are measured in routine practice, and by exploring any other age-related differences. real-world evidence may also provide insights on similarity of treatment strategies by reflecting routine clinical practices and potential age-related differences in terms of treatment choice, their sequence, dose, duration and response to treatment. Finally, pending the availability of relevant data, real-world evidence could also be explored for supporting the understanding of differences related to the absorption, distribution, metabolism and excretion (ADME), as well as differences between adult and paediatric populations in the pharmacological target, such as genetic differences. However, the usefulness of real-world data to support conclusions on disease similarity remains to be seen. If data on the relevance of the pharmacodynamics target, including data in support of a targets similarity across populations, is not available from real-world databases, it is rather unlikely that conclusions on disease similarity can be drawn based on real-world data only. However, real-world data can be utilised to support adequate study designs (Prilla et al., 2024). Besides, at the time of marketing authorisation application, there is often limited knowledge and evidence gaps on the long-term safety and effectiveness of medicines and medical interventions, which can also differ between paediatric and adult patients and can be challenging to address as part of clinical trials before authorisation. Regulators are now mandating additional measures to collect information during the post-authorisation phase, also using real-world evidence sources and requesting additional stratified analyses to generate more and better adjusted estimates to support in addressing these gaps (Post authorisation measures, 2009; Lasky & Chakravarty, 2022). Finally, real-world evidence can also be used to obtain data of consumption, and actual incidence and prevalence of the disease.

Using such data for regulatory purposes requires it to be reliable and fit for the purpose (Lasky & Chakravarty, 2022). Real-world evidence in general should be further explored for its utility supporting extrapolation discussions either within the extrapolation concept to further qualifying uncertainties or as part of the extrapolation plan in the context of the totality of evidence.

All in all, real-world data might complement the evidence generated during the clinical development and might contribute to better informed regulatory and HTA decision-making. The EMA and the European Medicines Regulatory Network have implemented a platform to collect evidence from real-world health-care databases across the European Union (EU) Member States and, although still in development, might be used in the future, also by HTA bodies. This platform is called the Data Analysis and Real World Interrogation Network (DARWIN EU®) (Big Data & EMA, 2021).

8 | CONCLUSIONS

We describe that extrapolation is a widely accepted and frequently used method to support paediatric medicines developments as it is ethically imperative to avoid the unnecessary enrolment of children in clinical trials. When properly proposed and justified, regulatory bodies often agree to its use. Throughout the medicine's life cycle, extrapolation (as per regulatory terms) seeks to gather the most relevant data, addressing uncertainties and progressively enrich knowledge over time to aid regulatory decision-making regarding the benefits/risks assessment. However, it is recognised that some uncertainties may only be resolved post marketing and/or in the real-world setting.

The general ambition is that paediatric investigation plans and the subsequent data generated within should also be sufficient to support further decision-making, such as by HTA bodies. With that said, within and across all relevant stakeholders involved in supporting access to paediatric medicines development, we have described the mutual awareness developed through the work within EUnetHTA 21 on the possibilities and challenges when agreeing to use extrapolation.

The need to further address gaps in evidentiary requirements between decision-makers is acknowledged (European Medicines Agency [EMA], 2021; EMA, 2023). This collaborative work has triggered discussions on how to best provide medicines life cycle management support for products addressing unmet needs in children in due time, appreciating a risk that in certain situations there will be remaining uncertainties at the level of HTA decision-making to be addressed, for example, as part of post-launch evidence generation.

It is an inevitable fact that compared to adults, uncertainties will in most cases be higher with any paediatric development, because of the increased variability, including pathophysiological differences and the limited population size, particularly in the youngest age subsets, such as neonates.

In Europe, the HTA regulation will ensure the generation of joint clinical assessments and present further opportunities for collaboration. Appreciating that the pricing and reimbursement decisions of medicines remain implemented at the national or regional level allows each country to assess new medicines, taking into consideration national needs, available therapeutic alternatives, budget constraints and organisational aspects.

Early interactions with all relevant stakeholders, particularly between regulators and HTA bodies are key to optimising data generation and its utility for paediatric populations as facilitated by collaborations through Joint Scientific Consultations (JSC) as detailed in the HTA regulation. This approach is vital for all developmental efforts. However, the unique challenges, which we explored and described associated with paediatric drug development, both ethically and in leveraging prior knowledge, as illustrated using extrapolation, present specific opportunities. These challenges offer the chance to refine methodologies for managing uncertainties throughout a product's life cycle. Such advancements can lead to further insights, ensuring that the most effective data are produced to support regulatory decisions and access to medicines.

8.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander et al., 2023).

AUTHOR CONTRIBUTIONS

All authors have been involved in the conceptional development of the manuscript, its drafting and critical revision. All authors have approved the final version.

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