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THEMED ISSUE REVIEW

Health technology assessment of paediatric medicines: European landscape, challenges and opportunities inside the conect4children project

Francesco Moretti[1] | Fabrice Ruiz[2] | Fedele Bonifazi[3] | Elena Pizzo[4] | Jenny M. Kindblom[5] | the c4c HTA expert group

[1]Arsenàl.IT—Centro Veneto Ricerca e Innovazione per la Sanità digitale, Padova, Italy

[2]ClinSearch, Malakoff, France

[3]Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Bari, Italy

[4]Department of Applied Health Research, University College London, London, UK

[5]Pediatric Clinical Research Center at the Queen Silvia Children's Hospital at Sahlgrenska University Hospital, Göteborg, Sweden

Correspondence
Francesco Moretti, Project Economist, Arsenàl.IT—Centro Veneto Ricerca e Innovazione per la sanità Digitale, Via N. Tommaseo 8/a, 35131 Padova, Italy.
Email: fmoretti@consorzioarsenal.it

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The medicine development process is complex and requires time and effort to ensure safety, efficacy and quality. In paediatrics, this process is even more challenging, as it involves a subgroup of the population that already faces a considerable gap in the clinical evaluation of medicines and devices compared to the adult population. Moreover, access to therapies is heavily influenced by national health technology assessment (HTA) recommendations, which often form the basis for pricing and reimbursement decisions that affect the availability of effective treatments within the national health systems. Yet performing an HTA to assess the relative effectiveness and cost-effectiveness of a new children's treatment has several non-trivial implications, creating a critical issue for the paediatric population. In addition, the advent of innovative health technologies for children emphasises the need to empower the role of HTAs in paediatrics. This article aims at describing the most relevant elements of the drug development process in the paediatric field by focusing on the HTA. Particular attention will be paid to the factors that influence market access for new paediatric medicines and patients' access to treatment. The article will also highlight some central methodological challenges in conducting HTA in the paediatric field. Finally, the article will provide insight into how initiatives, such as *conect4children*, may subsequently reinforce HTA awareness in the paediatric community and strengthen collaborations through network mechanisms.

KEYWORDS
access to treatment, drug development, health technology assessment, paediatric

1 | INTRODUCTION

Medicines development is a complex process that requires time and effort to ensure safety, efficacy and quality. In the paediatric field, this process is more challenging because it involves a subgroup of the population that sees a considerable gap in the clinical evaluation of medicines when compared to the adult population.[1,2] As an example, with approximately 100 million people aged under 19 years of age, children represent more than 20% of the European population. Despite this, more than two-thirds of marketed medicines are not labelled for use in the paediatric population and have yet to undergo the related testing and validations for use in children.[3–6]

Moreover, attention should not be limited to clinical trials for developing drugs, but should also focus on steps that are critical to bringing new medicines into daily clinical practice. In other words, focus should be paid not only to the efficacy of new drugs, but also to the processes that can affect market authorisations and drug reimbursements, which are key elements in ensuring equal access to treatments.[7]

In this regard, the health technology assessment (HTA), which is defined as "[a] multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system" is relevant.[8] The procedures for financing medicines can vary considerably between different countries, even within the European Union.[9,10] However, national authorities use HTA methodologies to inform decisions on pricing and reimbursement of medicines that have been granted market access[11,12] (see Figure 1). Specifically, HTA analyses are unique because they are based on comparisons with current treatment pathways to verify the relative efficacy of drugs, that is their ability to be more effective than the so-called "usual care".[10]

Although drug development and the subsequent processes for adopting new drugs into clinical practice are characterised by many elements, two broad categories can be highlighted for the sake of synthesis: *stakeholders*, or the subjects who are involved in the various processes for drug development; and *areas of interest*, which define the set of questions that emerge during each pharmaceutical evaluation.

Stakeholders are made up of a considerable number of subjects. They can include academic or research institutions; health and regulatory authorities; the pharmaceutical industry; patients, parents and their associations; or individual doctors and different healthcare professionals. The areas of interest category is particularly broad: a varied set of topics that refer to methodological, ethical, legal, social, economic, clinical and organisational factors.[13]

For these reasons, HTA evaluations play an important role in providing support to regulatory agencies for reimbursement decisions with respect to phases 3 and 4 of research in clinical trials.

This article aims to describe the primary elements that characterise the current context of the paediatric drug development process in paediatrics, with specific reference to the role that HTA analyses play in an area of study that has yet to be fully investigated.[14] Particular attention will be paid to the factors that influence market access for new paediatric drugs and patients' access to treatment. The paper will also highlight some central methodological challenges in conducting HTA in the paediatric field. Finally, the article will provide insight into how initiatives, such as *conect4children*, may subsequently reinforce HTA awareness in the paediatric community, strengthen collaborations (among all involved stakeholders) through network mechanisms and identify technologies in need of assessment.

In this perspective, this work constitutes one of the first contributions that the c4c HTA expert group intends to provide in the framework of its dissemination and communication activities. The HTA expert group, set up within the c4c project, is composed of different professionals. In particular, there are professionals from the following fields: HTA, health economics, management of drug development, different paediatric clinical areas and health policies.

2 | MARKET ACCESS AND ACCESS TO TREATMENT

The general drug development process is expensive and entails high risk and uncertainty due to the hit-or-miss nature of clinical research.[15] These factors are even more pronounced in the case of paediatric drugs for several reasons, including ethical issues, liabilities, small populations for some diseases and practical and technical challenges in conducting paediatric trials. Other factors include the inappropriateness of weight-based dosing, the absence of validated assessment measures and endpoints, the lack of a substantial market

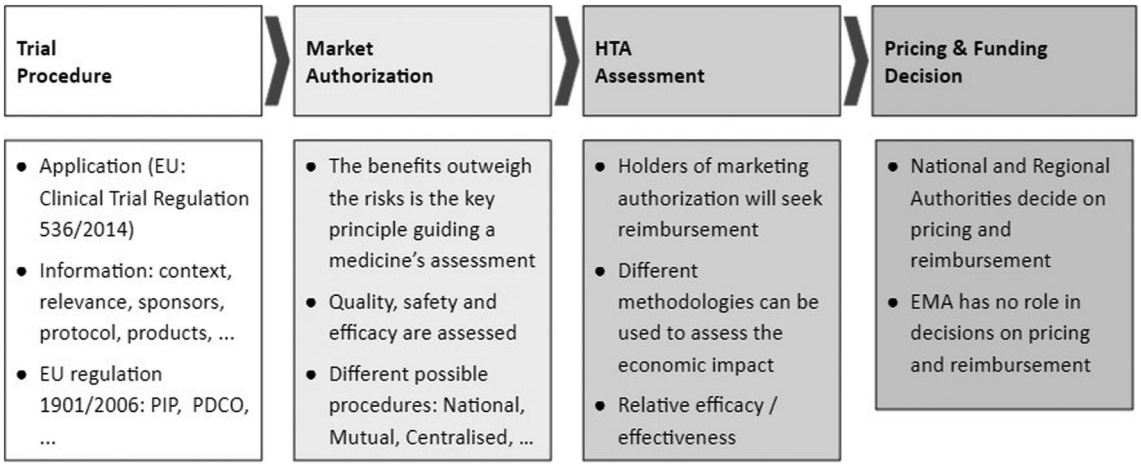

FIGURE 1 Key steps of the medicines development process and pricing and reimbursement decisions

and disincentives due to regulatory and market factors.[16] This is the case in Europe, where almost half the medicines used in paediatrics were being used off-label or off-license, and for one fifth of pharmaceuticals/devices sold to treat children, less than 10% were backed by paediatric clinical trials.[16] Appropriate formulation demand continues to be high. For example, the French healthcare authority has pointed to the need for paediatric formulations in several therapeutic areas, such as HIV/AIDS, attention-deficit disorders, rheumatology, osteoporosis, cardiac care, oncology and haematology.[16] The lack of paediatric tolerability and efficacy data have resulted in increased off-label prescriptions and allied risks. In addition to formulation aspects, the recommended dosing schedule, packaging, medical device type, ease of use or comprehensibility of instructions can impact the "intended use" of the medicines.[17] Other factors, such as ease of manufacture, logistics and availability of the required formulation also have a bearing on cost and access. It is evident that balancing patient acceptability, safety and access is difficult and often requires a compromise in formulation selection according to age.[18,19] Additional challenges to paediatric drug development include ethical, logistical, political, economic and regulatory issues in the context of conducting paediatric clinical trials.[20]

Over the past two decades, policymakers in Europe have introduced policy measures aimed at stimulating investments in paediatric drug development.[21–23] Laws to support economic incentives and making paediatric studies of new drugs mandatory in Europe have had a significant positive impact. The Regulation (EC) No 1901/2006 on medicinal products for paediatric use (the Paediatric Regulation [PR]) introduced a unified system of paediatric obligations and incentives to foster the development and availability of medicines for children. To compensate for manufacturers' effort in complying with the PR, medicines authorised across the EU, with results of studies from a paediatric investigation plan (PIP) included in the product information, are eligible for an extension of their supplementary protection certificate (SPC) by 6 months. Moreover, for orphan medicines, the incentive for including in the application for a marketing authorisation the results of all studies conducted in compliance with an agreed PIP is an additional 2 years of market exclusivity. The PR also introduced a paediatric use marketing authorisation (PUMA), which is a voluntary development pathway for off-patent medicine, used off-label in the paediatric setting that provides for an 8-year period of data exclusivity, followed by 2 years of market protection, subject to certain conditions.[24,25]

The European Medicines Agency (EMA) also grants paediatric investigation exemptions when the paediatric needs for the concerned condition are covered by existing products. These exemptions may also occur when the EMA Paediatric Committee (PDCO) agrees that the new product is unlikely to provide additional significant therapeutic benefit compared to existing therapies, thus avoiding unnecessary paediatric clinical trials.[24,25]

These initiatives, along with an increasingly sophisticated drug discovery and development process, have resulted in several advancements in paediatric drug labelling. In conjunction with the emergence of new drug targets, personalised medicine and regulatory innovations, this has nudged the drug development research focus to "for children" in contrast to "in children".[23]

There are several other important obstacles to industry investment in new uses for off-patent paediatric drugs. An example is the dismantling of pharmaceutical research infrastructure, as products near their patent and SPC expiry dates, thus curtailing further clinical/therapeutic development. In addition, currently practised reimbursement strategies in the market are unable to value the role of age-appropriate formulations in comparison to cheaper unlicensed alternatives. Policy experts also point out that the costs associated with an investment in furthering the product's life cycle, manufacturing and supply are inadequately compensated by the existing incentives.[23]

A 10-year evaluation of the European PR in 2016 reported that it has had a positive and significant impact on paediatric drug development with an increase in paediatric studies of investigational agents and labelling of paediatric information for use.[26] However, unintended consequences of existing policies and failures have also been identified. These include difficulties in starting, conducting and completing paediatric clinical trials (regulatory, economic, organisational, recruitment, etc.) and difficulties obtaining benefits provided by the regulation or benefits not matching the efforts required. Progress has been limited in certain therapeutic areas (e.g., neonatology, oncology) and for off-patent products.. Moreover, a recently published study assessed the marketing status in the Nordic countries of new medicinal products, authorised 2007–2016, reflecting the product availability following the PR. The study found that 21–32% of new medicinal products were not marketed,[19] and concluded that the implementation of the PR has flaws. In an ongoing review,[27] the European Commission is performing an evaluation of the PR and a subsequent impact assessment of different options to update the legal framework.[28] Future policy reforms, in addition to building on successes, will need to address these issues of concern.[23,26]

3 | METHODOLOGICAL CHALLENGES IN PERFORMING HTA IN THE PAEDIATRIC FIELD

Several policy measures aimed at stimulating investment in paediatric drug development have been introduced in Europe.[21–23] The 2006 Paediatric Regulation (PR) 1901/2006 introduced a unified system of paediatric obligations and incentives that facilitated the evaluation of newly authorised drugs.[24] Drug reimbursement decisions, at national level, are often contingent on health technology assessment (HTA).[29] HTA is a comprehensive evaluation framework that helps ascertain the value of new interventions, including medicines, diagnostics, medical devices and procedures. HTA evaluates safety, clinical utility, cost-effectiveness and also takes into account social, legal and ethical parameters, which are especially important in the case of vulnerable groups such as the paediatric population.[30,31] New medicines have limited clinical evidence and their clinical benefit is uncertain.[29]This is even more pronounced for paediatric medicines because the conduct

of paediatric trials involve several methodological, economic and ethical challenges.[20,32]

There is increasing awareness that current HTA approaches involve several problems in the context of paediatric health, ranging from methodological issues, such as standardisation of evidence appraisal and health economic evaluation criteria, to systemic issues, such as prioritisation processes for review and adjudication of technologies for public reimbursement approval.[30,33]

For example, when a medicine is to be approved for use in a paediatric population for similar indications as those approved in adults, it could be appropriate to extrapolate adult efficacy data. This is already legally required in Germany. Although this may seem straightforward, obtaining acceptance for the same (i.e., extrapolated) adult data for early benefit assessment by the German HTA body (G-BA) involves several challenges. This is because the G-BA re-evaluates similarity criteria even if they were previously accepted for market authorisation and applies additional criteria specific to German benefit assessments.[32,34]

Health economic evaluations often use quality-adjusted life years (QALY), which weight life expectancy by health-related quality of life, as a measure to guide decision making across therapeutic areas, patient populations and age groups. Measuring QALYs is difficult in children, especially in young children. The assumption that QALY gains are equal across varied populations could negatively impact the paediatric population if in reality the gains are smaller than in adults. This approach also does not take into account the possibility that society values health gains in children higher.[30,35] Furthermore, the paediatric population is not homogeneous and needs further subdivision (neonates, infants, adolescents, etc.). This makes the estimation of health state utilities, health outcomes and other parameters very challenging.[26] The techniques for evaluating paediatric health states are not standardised and challenges often arise because children are unable to self-evaluate and there are issues and biases that result when using proxy respondents (parents, care-givers, etc.).[36–38] Other equity issues concern the application of discounting to deferred costs and benefits to ascertain the present value. As is the case in many paediatric health programmes, the upfront costs are high while health benefits are deferred, thus potentially (unfairly) lowering the perceived health benefit.[30]

Conducting health economic evaluations of interventions (medicines, diagnostics, medical devices and procedures) for the paediatric population involves several challenges. Long-term outcomes and follow-up data are unavailable in most cases and therefore economists have to rely on model assumptions, inviting all their limitations.[36,39] Accurate cost data is also difficult to collect: especially when adopting a societal perspective, the number of variables to consider extends beyond direct costs (e.g., spillover effects—care-givers, family, long-term costs, etc.).[36] Uncertainty also poses an important challenge to the HTA process and has been shown to have significant impact on reimbursement decisions.[29,40,41]

The current HTA approaches are not well suited when dealing with paediatric health and illness and there is a need to develop innovative and sustainable solutions for the methodological challenges in value assessment.

In the period 1 January 2007 to 31 December 2020, 176 out of the 325 paediatric medicines approved by the EMA were authorised according to the provisions of the Paediatric Regulation (the remaining 149 are paediatric generics, biosimilars or hybrid products).[42]A search in the international HTA database hosted by INAHTA, the International Network of Agencies for Health Technology Assessment, shows that among its 17 656 records of bibliographic information about ongoing and published health technology assessments commissioned or undertaken by HTA organisations internationally, a positive match can be found for less than 40% of those 176 medicines, and full HTAs are only a minority.[43]

In some countries public access has been granted to the analyses that led to decisions on the clinical position of evaluated medicinal products, both in relation to market access and decisions guiding the determination and regulation of prices. Unfortunately, these analyses are not always available in English, which hinders comparisons for particular products across different markets.

In the case of France, the exchanges between national authorities HAS (Haute Autorité de Santé), and even those with representatives of pharmaceutical companies, are publicly available in full in French. In reading these exchanges, it would seem that evaluators find applications for paediatric medicines to be lacking in supporting studies. Indeed, during an HAS meeting on 13 May 2020, two separate evaluators emphasised that it was rare to obtain methodologically sound studies published in excellent quality journals included in filings for paediatric medicinal products.[44]

Moreover, obtaining a PUMA does not guarantee similar results in terms of reimbursement in different European countries. For example, during the evaluation of a hybrid drug (with a PUMA) for the treatment of a rare disease, the HAS emphasised: "the interest of making this new pharmaceutical form available and a new dosage that permits dose adaptations in paediatrics".[45] Despite this, the HAS simultaneously issued an opinion on the level of improvement offered by the new medication as "no clinical improvement" (*ASMR V*), indicating the absence of any "clinical added value". Nonetheless, the availability of this new dosage form adapted to paediatric practice seems to have been well received, with the reimbursed price of a 100 mg tablet in France (€0.57), whereas the reference product was sold at €0.76 for 500 mg tablets. In England, we find a similar ratio of £0.66 for the 100 mg paediatric tablet and £0.49 for the referent. But in Germany the arbitration board meeting[46] decided on a price almost 10 times lower for the 100 mg sachet (€0.064) while the price of the 500 mg tablet of the reference product is more expensive, at €0.93 (per 500 mg). This decision led to the withdrawal of the product from the market in Germany by the pharmaceutical company.

It would therefore appear that evaluators expect high levels of evidence from both the clinical and economic points of view, even in the case of a paediatric medicine for the treatment of a rare disease. This could be exemplified by the fact that, even with a dossier supported by excellent publications (two published in the *New England Journal of Medicine* and one in the *Lancet*), the applicant failed to

obtain the expected ranking with regard to added clinical benefits ("ASMR" levels). The evaluators (from the Commission Évaluation Économique et Santé Publique[47]) discussed the "most appropriate choices for estimating a meaningful ICER" (ICER stands for incremental cost-effectiveness ratio[48]), in particular, "the importance of anticipating uptake by caregivers in economic evaluations, from the initial design of the clinical trial or study, i.e. how caregivers will be included in the ICER calculations", as well as "the need for a standardised measure *for quality of life*, the EQ-5D".

4 | CONCLUSIONS

The previous sections presented the context in which HTA analyses are developed. In particular, two topics were investigated: (1) market authorisation and access to treatment, and (2) the methodological challenges of performing HTA analyses. In regard to the first topic, the elements of complexity in the drug development process were highlighted with specific reference to the high costs and nuances of the processes involved in paediatric cases.

The needs of the paediatric population differ significantly from those of the adult population. These factors determine potential market demand and require significant investment and focused analyses to verify the capacity to meet those needs. Recent legislation on the subject (i.e., EU regulations) has improved these circumstances by establishing a system of incentives, but it has yet to completely satisfy the demands of the paediatric population. Obligations, incentives and possibilities for deferral or exemption must also be matched with innovative approaches capable of assessing the socioeconomic impacts of the failure to address the specific needs of the paediatric population.

Regarding the second topic, the methodological challenges of HTA analyses were explored by highlighting the characteristics that make them difficult, such as issues related to recruitment, the exploitation of different data sources (e.g., observational and real-world data) and the identification of standards for endpoints. Other elements of interest, including the ability to assess long-term impacts on children's lives, are also essential in understanding the value of new treatments or health programmes in the paediatric population and providing a society-based point of view that accounts for spillover and unexpected consequences.

While not exhaustive in describing the many facets of the process leading to the introduction of a paediatric medicine into the market and its use in daily practice, the issues defined and explored in this article have highlighted some elements of interest. In particular, this article points out how methodological obstacles, administrative procedures and compliance with legislation, as well as the correct balancing of the interests at stake, represent a complex system of actors and rules.

One potential way to deal with this complexity is to exploit cooperation mechanisms. More specifically, through cooperation, it is possible to reduce information asymmetries and share knowledge and skills. The c4c network aims to offer a more efficient process, from clinical trials to daily clinical practice. Moreover, there is a second important objective: building a network capable of focusing the attention of the stakeholders involved on the priorities of the paediatric world. This begins with the engagement of the actors involved, but over time, it must leverage the commitment and reputation of the individual network members to increase the credibility of the network as a whole. In building c4c as a credible institution in the paediatric landscape, HTA plays an important role in the decision-making process that is necessary for effective and equitable access to treatments.

More specifically, the HTA process tends to be a bridge between the drug development process (the DD process) and the subsequent process used to determine the price of and reimbursement for (the P&R process) new medicines.

These two processes have distinct features and goals but also some common interests. On the one hand, we have clear incentives to avoid the cost of HTA evaluations of compounds that have high probability to fail. On the other hand, we have incentives to promote early discussions to prepare the information needed for the P&R process, shortening the time to reimbursement. For all those reasons, we already have some initiatives that aim to support the DD and PR processes, such as the EMA "Scientific Advice and Protocol Assistance" and the EMA–EUnetHTA "Parallel Consultation with HTA Bodies". The c4c initiative, with the HTA group, works in the same direction, but with a network mechanism aimed at facilitating paediatric clinical trials.

The HTA group within the c4c supports the quality and efficiency of both the DD and P&R processes. After a request from a clinical trial, collected by our single-point-of-contact infrastructure, the most suitable experts are quickly contacted and made available for discussions and challenges on the given topics. A report is then produced that includes the conclusions reached while maintaining the confidentiality of the information exchanged. Moreover, the HTA group experts are also involved in drafting white papers to raise awareness of the barriers to promoting paediatric clinical trials (see Figure 2).

There are therefore two different services linked to the activity of the HTA group: on the one hand, a concrete support for the development of clinical trials, taking into account the efficacy of the treatment, but also its value to the collective; and on the other hand, contributing to the debate regarding the challenges that limit the current development of paediatric clinical trials.

In summary, the next challenge for the HTA may be defined by two components: first, there is a need to contribute to the conduct of studies while considering the specific impacts of the introduction of new treatments on the paediatric population; second, there is a need to exploit cooperation mechanisms so as to identify the actual limitations of, and potential solutions derived from, providing valuable HTA to decision-makers.

COMPETING INTERESTS

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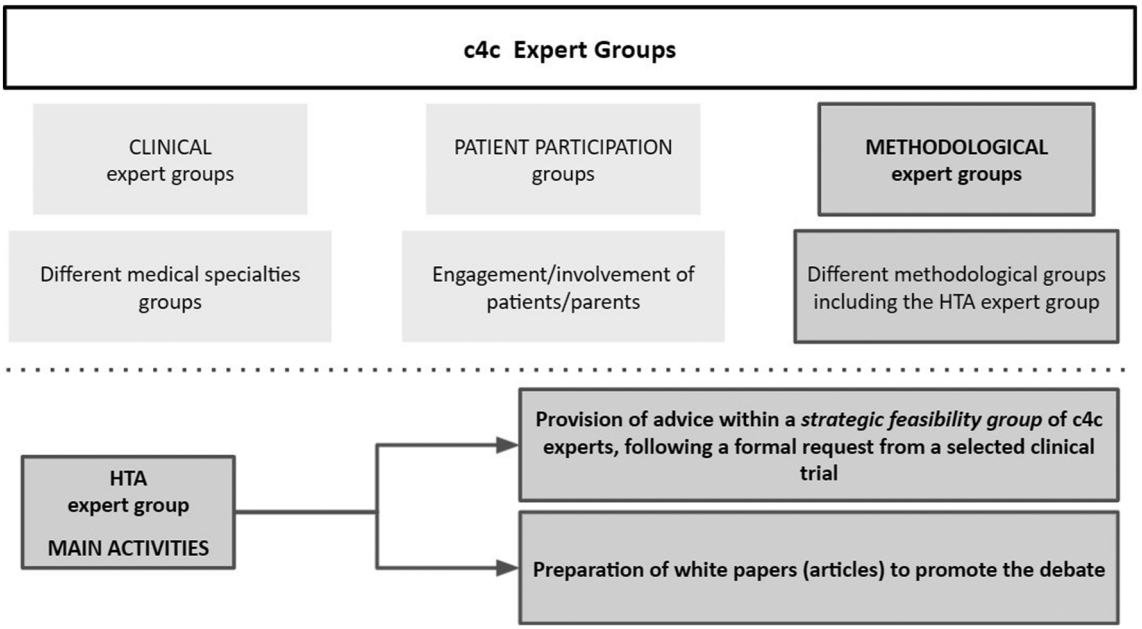

FIGURE 2 Main activities of the HTA expert group within the c4c initiative

(ARC) North Thames London. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Fabrice Ruiz is salaried by the contract research organisation ClinSearch, which develops and conducts evaluations for pharmaceutical and device companies. In particular, ClinSearch has worked for the company Orphelia Pharma, whose evaluation by the HAS is cited as an example. ClinSearch did not, however, participate in the development of the product concerned.

CONTRIBUTORS

F.M. and F.R. drafted the paper. F.B. and J.M.K. drafted and reviewed the paper. E.P. reviewed the paper. All authors contribute to the work of the c4c HTA expert group.

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ORCID

Francesco Moretti https://orcid.org/0000-0003-0947-7860

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