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EDITORIAL

Innovative methodologies in paediatric drug development: A conect4children (c4c) special issue

On average, half of all children in Europe take medicines, either for acute or chronic illness. At the same time almost half of these prescriptions are off-label, due to a historical lack of medicines specifically developed for children.[1] For ethical, practical and economic reasons, academic and industry researchers were reluctant to study drugs in children. With the 2007 EU Paediatric Regulation, and similar initiatives across the world, this situation has changed, as companies are now mandated to submit paediatric investigation plans early in the course of drug development. While these legislative efforts have resulted in a huge increase in the initiation of paediatric trials, new paediatric registrations have severely lagged behind.[2] Several causes can be identified, but a major reason for this disappointing result has been the failure to successfully perform paediatric clinical trials, not only in Europe, but across the world. Many studies were started but did not manage to recruit sufficient numbers of patients, and other studies failed to provide adequate answers on efficacy or safety due to suboptimal study design.

To overcome these challenges, the European Union with 10 pharmaceutical industry partners allocated, in 2018, €140 million for the conect4children (c4c) project through the public-private Innovative Medicines Initiative 2 (IMI2) funding programme.[3] The aim of this project is to provide better medicines for babies, children and young people through a pan-European clinical trial network. c4c aims to generate a sustainable infrastructure that optimizes the delivery of clinical trials in children through: (a) a single point of contact for all sponsors, sites and investigators; (b) efficient implementation of trials, adopting consistent approaches, aligned quality standards and coordination of sites at national and international level—to set up the network, three academic and at least four industry paediatric proof of viability trials will be run across the European network of over 20 countries and up to 300 sites; (c) collaboration with specialist and national networks; and (d) an education and training platform to shape the future leaders of paediatric drug development. The c4c Academy has been set up and is offering courses for good clinical practice, family and patient involvement, monitoring, trial start-up, paediatric investigation plan, innovative trial design, gene therapy trials, train the trainer, trial specific training, and paediatric drug development. Moreover, c4c aims to provide: (e) high-quality input into study design and preparation, through rigorous strategic and operational feasibility assessment and (f) the promotion of innovative study methodologies in clinical trial design.

For these two last aims—high-quality input in study design and preparation and the promotion of innovative trial methodology—c4c set up a European c4c expert network. This network exists of more than 300 experts organized into clinical subspecialty groups, innovative methodology groups and patient/parent representatives. During the course of paediatric drug development, investigators, either from industry or academia, can contact c4c to ask for strategic feasibility advice. This advice can encompass clinical, methodology and/or patient and public experts and will be provided through live or online meetings. In these expert meetings, involvement of patients and public reaches much further than advice on informed consent and assent forms and feedback of study results, but encompasses input in the actual study design including medical need, study endpoints, study procedures and planning of visits. To date, over 25 advice requests have been handled, involving all three groups of experts. Moreover, master service contracts with the industry partners and standing consultancy contracts with the experts have been arranged, overcoming one of the major roadblocks related to expert advice.

An important goal of this c4c activity is the implementation of innovative study methodologies in clinical trial design for feasible, high-quality, patient-friendly studies. c4c aims to reach this goal not only by providing advice on single drug development programmes or studies, but also by sharing the expertise of our innovative methodology expert groups. This special issue of *BJCP* is dedicated to presenting the state-of-the-art methodology for paediatric drug development, through a series of white papers from the methodology groups: Developmental Pharmacology, Pharmacometrics, Omics, Formulations, Health Technology Assessment (HTA) and Pharmacovigilance.

Developmental Pharmacology deals with the impact of growth and maturation on the disposition and effect of drugs.[4] This paper, co-written by experts from the c4c developmental pharmacology group and the European Society of Developmental Perinatal Paediatric Pharmacology, presents a state-of-the-art overview of major age-related variation in ADME (absorption, distribution, metabolism, and excretion) pathways, including drug metabolism and renal excretion and at the same time identifies important information gaps in need of further study. Using several target and disease-specific examples, the impact of ontogeny on the pharmacokinetic-pharmacodynamic (PK-PD) relationship is also illustrated, including preclinical models to study this relationship. The authors provide several suggestions to use this knowledge in drug development, including minimal invasive sampling, combined with metabolite profiling, application of age-specific assessment tools, preclinical models to study paediatric PD and abandoning the sequential age study design.

The US FDA (United States Food and Drug Administration) defines **Pharmacometrics** as the science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions. As presented by the pharmacometrics group, in paediatric drug development, pharmacometrics is importantly used to extrapolate data from adults to children to describe pharmacokinetics in children.[5] It has been used to inform paediatric trial design, in particular, to support paediatric dosing. Both, the bottom-up approach using physiology-based pharmacokinetic models, integrating paediatric physiology, as well as top-down methods, using adult and juvenile paediatric data, or mixed approaches are explained and discussed. Suggestions for a standard practice for paediatric pharmacometrics are presented.

A crucial aspect of pharmacotherapy is drug safety and **Pharmacovigilance**. Like the disposition and efficacy of drugs, the risk of experiencing adverse drug reactions is subject growth and development related variation. Children may be at a higher or lower risk of toxicity, or may develop age-specific adverse events. The detection of adverse events may also be affected by age. For example, headache in a non-verbal child may present as irritability and it will be hard to identify its exact cause. Aurich et al, present these child-specific issues and discuss methodological challenges during paediatric drug development, including considerations to be taken into account to overcome them.[6]

Neumann et al. discuss the need for and benefits of **Omics** approaches in paediatric drug development.[7] A better understanding of paediatric disease, the impact of ontogeny on drug disposition and effect, as well as the interplay of drugs with the disease warrants the use of Omics techniques. Omics approaches discussed are epigenomics, genomics, transcriptomics, proteomics, microbiomics and metabolomics. These omics studies are needed in children, as simple extrapolation of adult data ignores the impact of growth and development on these processes. The use of these techniques alone or in concert may aid the development of biomarkers to identify and treat subgroups of children. A strong call is made to include the collection of biological samples for omics studies in every paediatric clinical trial and also collect samples from healthy children.

Formulation scientists describe the global need for age-appropriate drug formulations. An extensive overview is presented on the current landscape of paediatric formulation development, and addresses major limitations and challenges, including regulatory.[8] The group presents a paediatric Quality Target Product Profile as an efficient tool to facilitate early planning and decision making across all teams involved in paediatric formulation development. Some key attributes for this tool are route of administration, paediatric age range, dosage form, dose/dose flexibility, patient acceptability, stability and patient access. The tool can be used during the paediatric formulation design phase, not only for new chemical entities, but also to repurpose/reformulate off-patent drugs. Moreover, the group calls for more collaboration between formulation scientists, manufacturers, clinicians and children, and for adding acceptability of formulations as major endpoints in paediatric clinical trials.

HTA is an important aspect of paediatric drug development and post-marketing use. The effectiveness and cost effectiveness of a drug is determined in order to support evidence-based decision making of both policymakers and healthcare professionals and an important use of HTA is decisions related to reimbursement. Moretti et al. describe paediatric-specific aspects related to value of medicines in the context of the regulations supporting drug development.[9] Moreover, they describe challenges related to HTA evaluations for paediatric medicines, including lack of long-term data, small study populations, but also differences in economics of treating children, including impact on families, society and the different weight quality-adjusted life-years may have in the evaluation of medicines for children. These examples may not only aid drug developers, but also research funders, national HTA bodies and patients/parents when prioritizing paediatric studies and deciding on reimbursement.

While conect4children is an EU-based project, the innovative methodologies presented, as well as the expert advice service, are not limited to c4c or strictly European clinical trials. Partnerships with similar US (Institute for Advanced Clinical Trials for Children, I-ACT for Children), Canadian (Maternal Infant Child and Youth Research Network, MICYRN) and Asian initiatives are underway. In 2021, the 16th Congress of the Asian Society for Pediatric Research specifically organized a paediatric clinical pharmacology session to allow experts from the c4c methodology groups to share their experience in innovative methodologies with clinicians and researchers in Asia. It is the strategic plan of c4c that the c4c expert advice service will become available to partners outside the consortium in the course of 2023 or early 2024.

In summary, this BJCP special issue provides state-of-the-art on innovative methodologies for paediatric drug development. We hope drug developers, in industry and academia, will use the guidance provided by these experts to design the best possible, innovative and child-friendly trials.

Further details of c4c can be found at https://conect4children.org/

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REFERENCES

1. Weda M, Hoebert J, Vervloet M, et al. *Study on off-label use of medicinal products in the European Union*. Luxembourg: Publications Office of the European Union; 2017.
2. European Commission. State of Paediatric Medicines in the EU: 10 years of the EU Paediatric Regulation. Published 2017. Accessed March 8, 2022. https://ec.europa.eu/health/system/files/2017-11/2017_childrensmedicines_report_en_0.pdf
3. conect4children. Collaborative Netwerk for European Clinical Trials for Children. Published 2018. Accessed March 8, 2022. https://www.conect4children.org
4. Smits A, Annaert P, Cavallaro G, et al. Current knowledge, challenges and innovations in developmental pharmacology: a combined conect4children Expert Group and European Society for Developmental, Perinatal and Paediatric Pharmacology White Paper. *Br J Clin Pharmacol*. 2022;88(12):4965–4984. doi:10.1111/bcp.14958
5. Bouazza N, Dokoumetzidis A, Knibbe CAJ, et al. General clinical and methodological considerations on the extrapolation of pharmacokinetics and optimisation of study protocols for small molecules and monoclonal antibodies in children. *Br J Clin Pharmacol*. 2022;88(12):4985–4996. doi:10.1111/bcp.15571
6. Aurich B, Apele-Freimane D, Banaschewski T, et al. c4c: Paediatric pharmacovigilance: methodological considerations in research and development of medicines for children—a c4c expert group white paper. *Br J Clin Pharmacol*. 2022;88(12):4997–5016. doi:10.1111/bcp.15119
7. Neumann E, Schreeck F, Herberg J, et al. How paediatric drug development and use could benefit from OMICs: a c4c expert group white paper. *Br J Clin Pharmacol*. 2022;88(12):5017–5033. doi:10.1111/bcp.15216
8. Walsh J, Schaufelberger D, Iurian S, et al. Path towards efficient paediatric formulation development based on partnering with clinical pharmacologists and clinicians, a conect4children expert group white paper. *Br J Clin Pharmacol*. 2022;88(12):5034–5051. doi:10.1111/bcp.14989
9. Moretti F, Ruiz F, Bonifazi F, Pizzo E, Kindblom JM. Health technology assessment of paediatric medicines: European landscape, challenges and opportunities inside the conect4children project. *Br J Clin Pharmacol*. 2022;88(12):5052–5059. doi:10.1111/bcp.15190