Innovative Methodologies in paediatric drug development: a conect4children (c4c) special issue

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Abstract

In this special issue of the British Journal of Clinical Pharmacology, we highlight innovative methodologies in pediatric drug development.

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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 historic 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 huge increase in paediatric trials to be initiated, 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, other studies failed to provide adequate answers on efficacy or safety due to suboptimal study design.

To overcome these challenges, the EU with 10 pharmaceutical industry partners allocated in 2018 140 million euros for the conect4children (c4c) project through the public-private IMI2 funding program[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; and c) collaboration with specialist and national networks; d) an education and training platform to shape the future leaders of 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 trial design and quantitative scientific methods.

For these two last aims: high quality input in study design and preparation and the promotion of innovative trial design, 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 PPI input and will be provided through live or online meetings. 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 does not only aim to reach this goal by providing advice on single drug

development programs or studies, but also by sharing the expertise of our innovative methodology expert groups. This special issue of BJCP is dedicated to present state of art methodology for paediatric drug development, through a series of white papers from the methodology groups: Developmental Pharmacology, Pharmacometrics, Omics, Formulations, HTA, and Pharmacovigilance.

Developmental Pharmacology deals with the impact of growth and maturation involved on the disposition and effect of drugs[4]. This paper, co-written by experts from c4c developmental pharmacology group and the European Society of Developmental Perinatal Paediatric Pharmacology presents a state of art overview of major age-related variation in ADME 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 PK-PD relationship is also illustrated, including pre-clinical 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 Agency) 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 largely used to extrapolate data from adults to children and to describe pharmacokinetics in children (REF). 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, growth and development impact the risk of experiencing adverse drug reactions. 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. E.g. headache in a non-verbal child, may present as irritability and it will hard to identify the exact cause of this irritability. 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[5].

Neuman et al. discuss the need for and benefits of **Omics**approaches in paediatric drug development (REF). A better understanding of the 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 includes, but is not limited to epigenomics, genomics, transcriptomics, proteomics and metabolomics. These studies are needed in children, as 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 to develop 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, but also to 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 address major limitations and challenges, including regulatory[6]. 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 for route of administration, paediatric age range, dosage form, dose/dose flexibility, patient acceptability, stability and patient access. The tool can be used during paediatric formulation design phase, not only for new chemical entities, but also to repurpose/reformulate off-patent drugs. Moreover, they call for more collaboration between formulation scientists, manufacturers, clinicians and children and for adding acceptability of formulations as major endpoints in paediatric clinical trials.

Health technology assessment (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 policy makers and healthcare professionals and an important use of HTA are decisions related to its reimbursement. Moretti et al, describe in their paper, paediatric specific aspects related to value of medicines in the context of the regulations supporting drug development [7]. 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 year 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.

In summary , this BJCP special issue provides state of art on 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 https://conect4children.org/

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