Controverse viewpoints: Controlled drug trials in children

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In the Pro and Con debate in *Lancet Haematology*, Christoph Male from the Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, argues for controlled drug trials in children. The example discussed is antithrombotic treatment with anticoagulants (blood thinners). Paul Monagle from the Royal Children's Hospital,

University of Melbourne, however, considers controlled studies for children with thrombosis barely feasible and not sufficiently informative. He favors dose finding and observational studies.

Male emphasizes that randomized controlled trials are the most valid method to demonstrate the efficacy and safety of a drug. However, particularly in children, such trials face several ethical, methodical, and practical challenges. If there are sufficient data on a drug available for license in adults, not all studies need to be replicated in children. Systematic extrapolation of adult data using innovative statistical modeling allows making predictions for dosing, efficacy and safety of a drug in children. Studies in children are still needed for validation, but in the context of pre-existing knowledge, require less children and, in some instances, studies may not be controlled. However, extrapolation is not possible if the disease or response to treatment is largely different between adults and children. In these situations, self-standing controlled trials in children are indispensable to evaluate the benefit-risk balance of a therapy for children.

Thrombosis (blood clot occluding vessels) occurs as complication of children with severe underlying diseases, such as cancer, heart defects, or prematurity. Thrombotic events can be taken as examples of rare disease, occurring in a diverse spectrum of children of different age groups. Accordingly, treatment studies are challenging in these patients and little solid evidence has been available so far.

Male quotes as successful example a controlled trial in 500 children with acute thrombosis comparing the new substance rivaroxaban versus standard anticoagulants, recently published in *Lancet Haematology*. The trial showed that treatment response in children was comparable to adults. "Thereby we learned that, for this indication, partial extrapolation appears possible, allowing for smaller pediatric studies in the future," says Male.

Another landmark trial of 950 children with leukemia and chemotherapy assessing anticoagulant prophylaxis of thrombosis was recently completed. Although controlled trials are not always feasible to the full extent, they should still be the centerpiece of drug evaluation in children, followed by observational studies during practical use.

Male's opponent, Paul Monagle, acknowledges the value of controlled trials in general, however, considers them barely feasible in children with thrombosis. In his opinion, controlled trials do not provide sufficient information for the various types of blood clots and different age groups. For the evaluation of anticoagulants in children, he considers dose-finding studies followed by observational studies more appropriate to reflect real-life clinical practice.

The European Medicines Agency (EMA) recognizes that high-quality data from studies in children are necessary for license of drugs for children. Therefore, EMA requires a Paediatric Investigation Plan for any new substance. For the development of Paediatric Investigation Plans, companies may receive scientific advice from EMA and their experts, such as Christoph Male.

More information: Christoph Male et al. Are controlled trials of anticoagulation in children feasible?, *The Lancet Haematology* (2020). DOI: 10.1016/S2352-3026(20)30043-0

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