CAUSALITY AND SEVERITY ASSESSMENT OF ADVERSE EVENTS IN PAEDIATRIC CLINICAL TRIALS: A LITERATURE REVIEW OF AVAILABLE TOOLS

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Introduction: Today we are well aware that the paediatric population presents a variety of different features compared to adults and that as a consequence, efficacy and safety data in children cannot necessarily be extrapolated from data in adults. With regards to the safety profile of a drug, in particular, the difference between children and adults may be particularly relevant. In fact, certain adverse drug reactions (ADRs) may only be seen in the paediatric population due to the maturation of organ systems, the metabolism, the growth and the development. Moreover, childhood diseases and disorders may be qualitatively and quantitatively different from their adult equivalents. Furthermore, children are not always able to communicate adverse effects clearly to their carers/health care professionals. The safety assessment in children and in the specific context of clinical trials is also particularly difficult because: a) the sample sizes are usually very low, and the size calculations are nearly always based on efficacy assumptions; and b) for many conditions the target paediatric population is relatively small and there may be a number of distinct age ranges to be considered. The Paediatric Clinical Research Infrastructure Network (PedCRIN) project brings together the European Clinical Research Infrastructure Network (ECRIN) and the most relevant European Networks and organizations in the field of paediatric clinical trials with the aim to build the necessary tools and capacity to enhance the high quality and ethical standards of multinational paediatric and neonatal clinical trials. One of the specific aims of the PedCRIN project is to analyse and implement age-adjusted tools to be used for ADR assessment in paediatric clinical trials. The starting point to address this aim was a systematic literature research to identify the already available tools for severity and causality assessments.

Material and methods: Starting from the search question "Identify the already available tools for assessing adverse events in paediatric clinical trials" and applying the PICO model, a literature search was conducted through the most widely used database in the biomedical community, MEDLINE (PubMed). No language restrictions were applied and the timeframe used was from 2012to 2017, seeing that a previous systematic review was carried out, with similar parameters, from 1966to 2011.

Results: A total of 718paediatric studies have been reviewed and only 154(7%) reported that a tool for causality assessment of adverse events was used. Sixty-eight of these studies (45%) did not specify the method used to assess causality, while among those studies that did report the algorithm employed for the evaluation of causality, the most used tool was the Naranjo Algorithm (25%), followed by the WHO-UMC system (6%). An interesting new causality assessment tool was identified: the Liverpool ADR Causality Assessment Tool (LCAT). The LCAT is an instrument developed by a multidisciplinary team at the University of Liverpool; it is in the format of a flowchart with dichotomous responses to each decision followed by routing to further specific questions. On the other hand, no specific scales were mentioned for the assessment of severity and a further research was required. The results of this supplementary search showed that the most used tools for determining severity were the Hartwig Severity Scale and Karch&Lasagna.

Discussion and conclusions: Our systematic review identified a lack of standardised methods to assess causality and severity of adverse events in the paediatric population. There is a strong need to design age-appropriate tools that could be used in this type of assessments and improve the efficiency of pharmacovigilance in the paediatric clinical research. Pilot trials could be then exploited to validate and implement these tools.