For an alliance between science, ethics and politics in promoting paediatric trials

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Abstract
After several decades during which children tended to be excluded from clinical trials, provisions to encourage trials with children have been in place for some years both at international level and in individual countries. The Nuffield Council on Bioethics has published a broad-ranging report on the subject, which makes concrete proposals for decision-makers and comes at a crucial moment in the definition of European Union regulations on this topic.

For some years now, attempts have been made to reverse the tendency to exclude minors from taking part in clinical trials, with many nations adopting legislation. The European Union, for example, adopted a Regulation on the matter in 2006 [1, 2].

The exclusion of minors sprang from the albeit commendable intention of protecting particularly vulnerable individuals from possible risks, but has proved to be a serious obstacle to the development of drugs for use specifically in paediatrics. In other words, the intention of protecting minors from the risks deriving from trials has excluded those same minors from the possible benefits to be gained from such research. This has led to the widespread use of off-label drugs in paediatrics in both primary and hospital care [3]. A large study in Sweden found that approximately 70% of all drugs given to neonates in hospital care were off-label, non-approved drugs or drugs insufficiently documented for the specific age group [4].

Several institutions have published extensive reference papers and guidelines regarding the scientific and ethical principles involved in the conduct of clinical trials with children, two examples being the US Institute of Medicine’s “The ethical conduct of clinical research involving children” [5] and the British Medical Research Council’s “Medical research involving children” [6].

Such documents usual agree that paediatric trials should be allowed only when certain requisites are satisfied. More specifically, trials may be acceptable: if they are directly associated with a clinical condition affecting the interested minor, are of such a nature that they can be conducted only with minors and not with legally competent persons, and are conducted in full compliance with the principle of the child’s best interest; if they are intended to study treatments for a clinical condition that affects only minors, or are necessary to convalidate in minors findings obtained in clinical trials involving subjects able to provide informed consent; if the benefit to the interested minor is greater than the associated risks or burdens; if, where the aim is to achieve a benefit for the population that the minor represents, the risk for the interested minor is minimum in relation to the standard treatment adopted for his or her condition; if informed consent has been obtained from the person(s) having parental responsibility or from the legally appointed representative; if a minor who has reached an adequate level of intellectual capacity is actively involved in the informed consent procedure.

One of the more delicate aspects concerns the balance between the benefit to the individual and the scientific interest in acquiring new knowledge that may be useful for the treatment of future patients. Ethical documents agree that the former should take precedence over the latter, as the WMA’s Declaration of Helsinki clearly asserts: “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects” (Article 8) [7]. The interpretation and application of this principle are nonetheless not without ambiguity, as attested by the fact that the “Report of the International Bioethics Committee of UNESCO (IBC) on consent” states in paragraph 87 that “Research activities involving children are carried out to learn more about the nature of paediatric development, disease and
potential treatments. Though one might hope that it will in some cases be beneficial to the research participant, the activity cannot be said to be specifically designed for this purpose because of the nature of the research question" [8]. In this context it is worth mentioning the recent report by the Nuffield Council on Bioethics "Children and clinical research: ethical issues" [9]. The Nuffield Council on Bioethics is an independent body that examines and reports on ethical issues in biology and medicine and that has achieved an international reputation for advising policy makers. The report [9] was prepared by a working group set up in 2013 and is the product of consultations involving over 500 experts from around the globe. The final recommendations are concerned in particular with: the adoption of simple but efficacious regulations to facilitate paediatric research; the balance between parental consent and the assent of the minor; the promotion of transparency in procedures, also with a view to encouraging the exchange of scientific information and data; the adoption of strategies that increase public awareness of the need for clinical trials. Rather than adding yet another checklist on the ethical acceptability of paediatric research, the Nuffield Council’s report is an attempt to submit a series of recommendations to the institutions concerned. Among its recommendations, for instance, are proposals: that the Royal College of Paediatrics and Child Health act to ensure that “outcomes of “innovative” or “experimental” treatment given to children and young people outside the context of research is properly documented”; that institutions “establish a database of experts”; that Parliament take appropriate measures to increase public awareness concerning paediatric trials; that the European Medicines Agency’s Paediatric Committee review the class waiver system that exempts certain categories of drugs from the requirement to include young people in clinical trials.

The significance of the Nuffield Council’s recommendations beyond the borders of the United Kingdom is due not only to their applicability in different contexts but also, in the case of EU Member States, to the current situation in the European Union. On 16th June 2014 “Regulation (EU) 536/2014 of the European Parliament and of the Council of 16th April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC” [10] entered into force. This will become fully applicable after 29th May 2016 (but in any case not before a new single data base for all member states, as provided for in the Recommendation, enters into operation). This is thus a propitious moment for individual states, as well as the European Union as a whole, to adopt scientifically and ethically solid procedures to encourage paediatric trials.

Conflict of interest statement
None to declare.

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REFERENCES