

**Response to European Commission report on the Paediatric
Regulation: consultation document**

February 2017

Introduction

- 1 The Nuffield Council on Bioethics is an independent UK body that examines and reports on ethical issues arising from developments in biological and medical research that concern the public interest. We welcome the opportunity to respond to the European Commission's consultation document on the Paediatric Regulation.
- 2 The Council's response draws on the conclusions of our report *Children and clinical research: ethical issues*, which was published in May 2015, to address five of the Commission's consultation items. The full report is available at <http://nuffieldbioethics.org/project/children-research/>. More information about the Council and about this report is annexed.

Response

Consultation item 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

- 3 We firmly believe that children and young people are best-protected from ill-health, disease, and the impacts of disability through a greater commitment to evidence-based treatments. At present, the evidence base for care offered to children and young people falls behind that for adults: clinical research involving children is essential if we are to improve our understanding of childhood diseases and conditions, and provide care for children and young people based on the best possible evidence. We therefore encourage and support specific legislation to support the development of paediatric medicines.
- 4 We note further that since the Paediatric Regulation came into force in 2007, it has made a real and welcome difference to the amount of evidence available to prescribers on the effects of medicines on children and young people.

Consultation item 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

- 5 We are concerned that the waiver system as set out by Article 11 of the Paediatric Regulation is not working as originally intended. Many adult disorders, such as some cancers, do not have direct equivalents in children, but – as the consultation

document notes – this does not mean that the mechanism of action of the medicine being developed will not be effective in treating related disorders in children. For example, the Institute of Cancer Research (UK) notes that 26 of the 28 cancer medicines authorised in Europe since 2007 have a mechanism of action that is relevant for childhood cancers; nevertheless, 14 of these medicines received waivers.¹ A loss of opportunity to promote such research, which is potentially important for children’s health, is a matter of ethical concern.

- 6 We therefore welcome the EMA’s 2015 review of class waiver decisions,² and its encouragement of a voluntary approach to carrying out research with children (see *paragraph 5.45 of our full report*). We note and encourage the EMA Paediatric Committee’s (PDCO) commitment to continue to revise the class waiver list as more information on medicines and diseases become available.³

Consultation item 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

- 7 We note that the PUMA concept has had very limited success. We suggest three approaches through which the development of off-patent medicines for paediatric use might be further developed:

- Considering a model of ‘transferable market exclusivity’, where the successful completion of a paediatric investigation plan (PIP) with respect to an off-patent medicine will allow the value of the incentive to be transferred to a different product. Any such incentive would need to be carefully targeted to ensure that it is limited to cases where there is a clear need for the research; this could, for example, be achieved by linking it to the EMA’s inventory of priority needs, or by giving PDCO the discretion to accept or reject the proposal on the basis of need. (See *paragraph 5.46 of our full report*.)
- Using tax breaks, if necessary on a country-by-country basis. (See *paragraph 5.46*.)
- Encouraging collaborative research between academic researchers, patient groups, and industry, in the light of the fact that industry is not the only possible source of research activity with respect to off-patent medicines in children. (See *paragraphs 5.47-8*.)

Consultation item 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

- 8 We welcome the significant benefits that the Paediatric Regulation has brought by increasing the focus on medicines research with children in a European context.

¹ See: <http://www.icr.ac.uk/news-archive/icr-scientists-call-for-changes-to-eu-rules-on-children's-cancer-drugs>.

² See: <http://nuffieldbioethics.org/news/2015/promoting-medicines-research-children-council-welcomes-emas-review/>.

³ See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002375.jsp&mid=WC0b01ac058004d5c1.

We recognise in particular the positive and proactive approach the EMA and PDCO have taken to their regulatory role, using it not only to police the system established by the Regulation, but also to promote effective and collaborative research with children and young people through a variety of practical means. We encourage the EMA and PDCO to continue to build on these successes, and to use the opportunity of the ten-year review to identify need for legislative change.

- 9 We note the findings of the 2013 European Commission report which reviewed the impact of the first five years of the Paediatric Regulation, and the progress it reported since the Regulation was passed.⁴ Progress includes the agreement of over 600 PIPs by PDCO, thus ensuring that information would be collected about the efficacy and safety of these medicines in children; additionally, the introduction of 132 new medicines, or new uses of existing medicines, licensed or adapted for children. However, as the consultation document notes, “so far the exact impact [of the Regulation] on the number of paediatric trials and study participants is difficult to quantify due to some shortcomings in the available databases with regard to mandatory data.” By addressing such shortcomings, the 10-year review of the Regulation will be integral to revealing whether such progress has continued to be realised.
- 10 We agree that the Regulation has fostered and stimulated expert discussions on the optimal design of paediatric trials. We particularly note that although – according to the Commissions five-year report on the Regulation – the number of clinical trials involving children remained fairly constant at an average of approximately 350 per year, this in fact represented a small increase in the proportion of clinical trials involving children, as the total number of trials taking place had been falling. Medicines research with children in a European context is now part of the mainstream: research sponsors are required to develop PIPs as routine (unless a waiver has been granted); medicines targeting new indications in children are beginning to become available; the quality of children’s clinical trials is improving; and there is more innovative thinking in the development of medicines for children (*see paragraph 5.43 in our full report*).
- 11 However, areas remain where the Paediatric Regulation might make further improvements. These include the use of class waivers with respect to research that might still be of benefit to children; addressing the ineffectiveness of incentives that seek to encourage research with children on older off-patent medicines (*see paragraph 7 of this response*); and the question of how best to incentivise research in conditions that only, or primarily, affect children (*see paragraphs 3.18-3.22 in our full report*).

A note on ‘vulnerability’

- 12 The consultation document notes the importance that “everything possible is done to make sure that the specific vulnerability of child patients is fully considered”. We urge a degree of caution around the language employed. In our report, we noted how the regulation of clinical research with children and young people is often

⁴ European Commission (2013) Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality, available at: <http://www.ipex.eu/IPEXLWEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>.

based on this assumption that, by their nature, children and young people constitute a 'vulnerable group', and that such vulnerability automatically demands a protective response. In our evidence gathering we heard concerns that this apparently protective response to perceived or actual vulnerability may not only exclude children and young people from opportunities to participate in activities that are inherently worthwhile, but could also *harm* the interests of many children in the future by preventing potentially valuable research from taking place. We would emphasise that the possibility of vulnerability rests in the situation that a person is placed in, not necessarily in the person himself or herself. References to vulnerability in the context of children and young people's involvement in research should never be treated as an automatic brake on a research proposal. We suggest that an appropriate response by professionals to concerns about children's potential vulnerability in research is to ensure that they work in partnership with children, young people and parents throughout the whole endeavour of research.

Consultation item 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

- 13 We feel that the Paediatric Regulation has had a positive effect on paediatric research in Europe for the reasons set out in paragraphs 8-10 above.

Conclusion

- 14 The Council thanks the Commission for the opportunity of submitting its views on this consultation. For further information on the Nuffield Council's response to this consultation, please contact: Katharine Wright (Assistant Director, Nuffield Council on Bioethics) at kwright@nuffieldbioethics.org.

ANNEX

The Nuffield Council on Bioethics Working Party

The Nuffield Council on Bioethics is an independent UK body that examines and reports on ethical issues raised by developments in biology and medicine. It is funded by the Nuffield Foundation, the UK Medical Research Council, and the Wellcome Trust. For more information about the Council see: www.nuffieldbioethics.org.

The Nuffield Council on Bioethics' Working Party on children and clinical research was set up in June 2013, and its report, *Children and clinical research: ethical issues* was published in May 2015. More information about the evidence gathering of the Working Party is available at <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

Members (affiliations correct at May 2015)

Bobbie Farsides (Chair) - Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School

Joe Brierley - Consultant in Paediatric and Neonatal Intensive Care at Great Ormond Street Hospital

Imelda Coyne - Professor of Children's Nursing at Trinity College Dublin, Ireland

Elizabeth Davis - Paediatric Nurse at the John Radcliffe Hospital, Oxford

Sara Fovargue - Reader in Law at Lancaster University

Robin Gill - Professor of Applied Theology at the University of Kent

Roland Jackson - Executive Chair of Sciencewise

Vicki Marsh ('job-share' with Sassy Molyneux) - Senior social science and public health researcher at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

Sassy Molyneux ('job-share' with Vicki Marsh) - Senior social scientist at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

Helen Sammons - General Paediatrician (Derbyshire Children's Hospital) and Associate Professor of Child Health at the University of Nottingham

Mark Sheehan - Oxford NIHR Biomedical Research Centre Ethics Fellow at the Ethox Centre and a Research Fellow at the Uehiro Centre for Practical Ethics, University of Oxford

Susan Tansey - Medical Director (Paediatrics) at Premier Research Group Limited and Associate Director for Industry for the NIHR-CRN: Children (formerly Medicines for Children Research Network).

Marc Taylor - Chair of ISRCTN, a not-for-profit organisation that manages the unique identification of randomised controlled trials worldwide

Bridget Young - Professor of Psychology at the University of Liverpool.