

MEETING REPORT

European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children

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Abbreviations: CORE-MD, Coordinating Research and Evidence for Medical Devices; EAP, European Academy of Paediatrics; EU, European Union; FDA, US Food and Drug Administration; MDR, Medical Device Regulation; RCT, Randomised controlled trial.

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Abstract

Several high-risk medical devices for children have become unavailable in the European Union (EU), since requirements and costs for device certification increased markedly due to the EU Medical Device Regulation. The EU-funded CORE-MD project held a workshop in January 2023 with experts from various child health specialties, representatives of European paediatric associations, a regulatory authority and the European Commission Directorate General Health and Food Safety. A virtual follow-up meeting took place in March 2023. We developed recommendations for investigation of high-risk medical devices for children building on participants' expertise and results of a scoping review of clinical trials on high-risk medical devices in children. Approaches for evaluating and certifying high-risk medical devices for market introduction are proposed.

KEYWORDS

children, clinical evaluation, clinical investigation, expert workshop, high-risk medical devices, recommendations

1 | INTRODUCTION

Putting a broken arm in plaster, delivering drugs and fluids via an infusion pump, or implanting a prosthetic heart valve to replicate native valve function: These medical interventions would not be possible without the use of medical devices. In the European Union (EU) the Medical Device Regulation (EU 2017/745; MDR) aims at ensuring the safety and efficacy of medical devices by regulating their approval for introduction to the EU market.¹ Medical devices are defined as 'products or equipment intended for a medical purpose'.² Their risk classification is based on their properties and the assumed risk posed to the patients.³ High-risk medical devices include implantable devices and active devices 'that are intended to administer or remove medicinal products from the body'² such as pacemakers, vascular stents or closed-loop-insulin delivery systems.

Recently, European clinicians and their associations have expressed concerns about serious shortages of some paediatric high-risk medical devices in the EU. A report on orphan medical devices and paediatric cardiology and a survey on the availability of medical devices by the Biomedical Alliance in Europe indicate that a large number of devices that are essential for treating sick children have been withdrawn from the market.^{4,5} Examples are balloons for performing the life-saving Rashkind manoeuvre in newborn infants with certain congenital heart defects, or a lack of adequately equipped haemodialysis machines in young children with end-stage kidney disease.^{4,6} Manufacturers indicate that devices are being withdrawn from the market because they cannot shoulder the increased regulatory requirements that result from implementation of the EU MDR,¹ whose original goal was to ensure the safety of patients.

The project 'Coordinating Research and Evidence for Medical Devices' (CORE-MD) is an EU Horizon 2020 funded project that reviews methodologies for the clinical investigation and evaluation of high-risk medical devices. It aims to recommend an appropriate balance between clinical efficacy, safety, innovation and availability for meeting patient needs.⁷ One of the project's objectives is to develop recommendations on the clinical investigation and evaluation of high-risk medical devices for infants, children and adolescents. The task is led by the European Academy of Paediatrics (EAP), the umbrella organisation for paediatric national and subspecialty associations in Europe. As part of this task, EAP hosted a high-level expert workshop on 16 January 2023 at Ludwig Maximilian University Munich, Germany, followed by a further virtual meeting on 23 March 2023. Here we report the aims and conclusions of the workshop. Developed recommendations represent the expert opinions of the clinical experts.

2 | AIMS AND OBJECTIVES OF THE WORKSHOP

The first objective of the workshop was to develop recommendations for appropriate methodologies for clinical investigation of high-risk medical devices for use in children. The second objective

was to comment on approaches for evaluating and certifying high-risk paediatric medical devices for market introduction, aiming both at documenting safety and at ensuring continued availability of devices important for treating sick children.

3 | METHODS

Relevant paediatric experts using, investigating or evaluating high-risk medical devices were identified through the collaborative networks of the EAP and the CORE-MD consortium. At the end of July 2022, potential experts and advisors were invited to join the expert panel. Additionally, European professional paediatric associations/societies were invited to nominate representatives for participation. We established a multi-stakeholder expert panel with 20 paediatric experts/regulatory advisors from eight European countries (Belgium, Croatia, Finland, Germany, Ireland, Italy, Poland, United Kingdom). The participating experts included clinicians and representatives of European paediatric subspecialty associations from the field of cardiology, endocrinology, neonatology, gastroenterology, surgery, nephrology, oncology and interventional radiology. In addition to the experts, a regulatory authority representative and an officer from the European Commission Directorate General Health and Food Safety (DG SANTE) participated by providing regulatory information, advice and context.

To assist the experts in recommendations development, EAP charged the Child Health Foundation at LMU (Stiftung Kindergesundheit) to perform a scoping review on evidence from clinical trials investigating high-risk medical devices in children (Guerlich et al., under review).⁸ Key review findings shared with the workshop participants in advance, were based on the evaluation of a sample of 99 included clinical trials. Most of the identified trials were multicentre and conducted in Europe and North America. Medical devices used as an intervention were mainly from the clinical specialty of diabetology (88%). Sample sizes were mainly small, often <100 participants. Within the analysed sample, most of the studies included adolescents, whereas only 3% of studies enrolled infants (together with children from other age groups). Around 40% of studies evaluated the device of interest in a mixed population of both children and adults. 38% of studies were randomised controlled trials (RCTs). Other study designs applied included crossover trials, before and after studies and uncontrolled trials. Device efficacy/effectiveness and safety were the most frequently assessed outcomes.

In preparation for the workshop, EAP shared key questions (Appendix S1) on the requirements for the level of evidence supporting paediatric medical devices, definition of orphan medical device, and optimal strategies for marketing authorisation of high-risk medical devices for patients in the paediatric age group.

The workshop was introduced with presentations providing an overview on the paediatric medical device context. These included medical device classification, the European system for the evaluation and approval of high-risk medical devices, current regulations, Commission's proposal for the amendment of the transition period

of the EU MDR (2017/745)⁹ and non-legislative actions. CORE-MD project background and objectives were also provided.

4 | RESULTS

4.1 | Barriers for market access of high-risk medical devices in Europe

The clinical experts agreed that the EU MDR has led to creation of higher barriers for market access of high-risk medical devices, particularly for children and other patients with rare diseases. This will result in some manufacturers not pursuing conformity assessment, particularly for products with a small market volume and hence small financial profits, including most products used in children. The barriers include the need for providing data from clinical investigation, which often is hardly feasible for products used only in small numbers of patients. An additional concern is the apparent current lack of involvement of paediatric experts in the evaluation process by most notified bodies, although this clinical expertise is essential for a competent review of products used in children. Furthermore, the time to obtain certification is expected to last between 18 and 24 months,⁴ because of the very limited number and capacity of notified bodies to assess the large number of medical devices.^{9,10} Finally, a major barrier for enabling the appropriate availability of medical devices for the paediatric age group is the very high financial cost of their assessment. This arises from the delegation of the conformity assessment in the EU to profit-making private enterprises that serve as notified bodies, with no prerequisites taken to encourage the certification of paediatric or orphan devices at low cost. In contrast, in the EU and USA pharmaceuticals are evaluated by public bodies, and proactive strategies were developed to encourage the development, testing and market introduction of pharmaceuticals for paediatric patients as well as orphan drugs for rare diseases.¹¹ Recent report indicated that the cost for regulatory assessment of a single device in Europe is multiple times higher than by FDA. For instance, the costs for the Z-5/Z-6 Atrioseptostomy catheters regulatory assessment in Europe is €135 844 every 5 years compared to €3030 for the lifetime market access in the USA.⁴

4.2 | Off-label use of medical devices in children

Medical devices designed and marketed for adult patients are regularly used off-label for different purposes in children.¹² For example, stents developed and used for treating bile duct stenosis in adults are used for treating small vessel stenosis in young children. Clinicians using a device under such conditions take responsibility for the off-label use, while uncertainties exist regarding potential liability. The experts emphasised the need to better define the conditions of off-label use, and to provide a framework for clinicians acknowledging when such off-label usage is appropriate and acceptable. The MDR

(Annex XIV, part B, section 6.1(e)) indicates that manufacturers should seek to identify 'possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct'.¹ The experts recommended to establish a framework for manufacturers guiding them in collecting data, if their device is being used in an off-label manner for an essential intervention, in cases where there are few available alternatives or as a 'last option' device. A supportive regulatory framework should facilitate certification of devices for such alternate uses with the limited data that may be available, indicating a roadmap to generate the data and approve the device for the paediatric intervention. European paediatric associations, in collaboration with manufacturers, rare disease networks and patient organisations, should collect data on off-label use of medical devices in a structured way.

4.3 | Aspects of clinical evaluation of medical devices and proposed approaches

Uniform regulatory rules worldwide would be desirable even though they may be difficult to achieve. There is a need for equivalent regulatory standards in the major markets around the globe to prevent a move of medical device development and manufacturing away from the EU. Strategies are needed that proactively encourage and facilitate the development, evaluation and market introduction of innovative medical devices for children. These could be similar to support provided in the EU for orphan pharmaceutical products¹¹ or to the Paediatric Device Consortia Grants Program of the US Food and Drug Administration (FDA).¹³ When devices are not introduced to the market because of their limited sales volumes and profitability for manufacturers, public co-funding is required to protect the rights of children with orphan diseases to obtain the best possible medical devices for the treatment of their conditions. A priority regulatory pathway¹⁴ with a defined short timeline, similar to that established in the USA for Humanitarian Device Exemption,¹⁵ and with special low assessment fees should be introduced. A few (private enterprise) notified bodies in the EU could be designated to evaluate orphan medical devices, with their costs subsidised by public funding. Alternatively, a public body similar to the European Medicine Agency could be established at the EU level or by one or more member states, with responsibility for the evaluation and registration of orphan medical devices at low cost.

An expert panel focussing on paediatric medical devices should be established that needs to include paediatric experts. It should be charged with providing scientific and clinical advice to the EU Medical Devices Coordination Group on the consistent application of the MDR with respect to medical devices used for children in accordance with Article 106 of the MDR. Additionally, it should determine whether a high-risk device is designated to have orphan medical device status. The group supported defining an orphan medical device on a case-by-case basis by an expert panel that involves competent paediatric experts, similar to the practice of the Humanitarian Device Exemption Regulation in the USA. One but not

the only requirement is that the device should be used in a rare disease as defined in the EU legislation, for example a 'life-threatening or chronically debilitating disease' with a prevalence of <1 per 2000 people.¹⁶ Other currently discussed cut-off points do not have a reference in EU law to justify them. Additional criteria to be considered by an expert panel in granting an orphan medical device designation should include an unmet need and an absence or insufficiency of suitable alternative therapeutic options with expected similar clinical benefit and safety. The expert panel to be established should also provide advice to developers of high-risk medical devices in accordance with MDR Article 61 (2).¹ Manufacturers should get the possibility to obtain scientific advice and feedback on their investigational protocol from notified bodies and involved paediatric experts before starting a clinical trial on a medical device. Collaboration between clinicians and manufacturers is needed to create and document clinical data on the use, suitability and safety of medical devices. An agreement needs to be developed on requirements for clinical investigation of medical devices for children, for which collaboration of paediatricians and paediatric surgeons with regulatory specialists is essential. Involvement of patient representatives and the inclusion of patient-reported outcomes, together with guidance development on their engagement in clinical studies' design and conduct, is favoured. Notified bodies who certify paediatric medical devices should be required to include advice from competent paediatric experts.

The experts emphasised that transparency of both the advice of expert panels concerning clinical evidence expectations provided to device developers in accordance with Article 61(2),¹ and the clinical data relied upon by manufacturers for paediatric medical devices, is necessary to ensure that developers can predict clinical evidence requirements. Additionally, healthcare practitioners should have access to the often limited clinical data relating to the device.

4.4 | Challenges of conducting clinical trials on high-risk medical devices in paediatric population

The findings from the scoping review on the evidence from clinical trials on high-risk medical devices in children (Guerlich et al., under review), reflect important challenges in this research area. Most published investigations were performed in adolescents, which points to greater barriers of gathering clinical evidence on high-risk medical devices in infants and young children. Likely reasons for the limited patient enrolment in such studies include the overall relatively small number of patients in younger age groups that require medical devices, and the low prevalence of many of the diseases of interest such as specific types of congenital heart defects.¹⁷ Also ethical considerations, and parental concerns on participation of infants and young children in clinical studies and challenges to obtain informed consent from parents, particularly under stressful emergency situations with limited time prior to an urgent intervention, can limit recruitment of young patients into studies.¹⁵ This should lead to special considerations for regulatory approval of high-risk medical devices for infants and young children.

Most studies identified by the scoping review were performed on devices for diabetic patients in adolescence. This shows that in this clinical speciality it might be feasible to conduct clinical trials because more paediatric patients with this relatively common disorder are available, and the devices used are basically identical to those used in adults. It appears to be more attractive for manufacturers to perform studies on devices with large sales volumes, in conditions with a high prevalence and long-term use of the devices and related consumables over many years. This can provide a significant profit margin, while there is no need to perform separate studies on devices specifically developed for infants and young children with low sales volumes. However, for other diseases with a lower prevalence and therefore a small number of patients, it may not be feasible to conduct informative controlled clinical trials. One example reviewed in the workshop was the life-saving Rashkind manoeuvre, an emergency procedure with a balloon catheter in newborn infants with certain congenital cyanotic heart defects. A limited number of infants require such an intervention, and the anatomic and clinical situation can be rather different between patients, making it difficult to conduct adequately powered controlled clinical trials. In situations like this, a combination of clinical information from case series along with post-marketing surveillance with longer-term follow-up in registries could demonstrate sufficient effectiveness and safety of the devices under question, without unduly denying sick children access to required medical interventions.

4.5 | Protection of children rights and ethical aspects of clinical investigation of medical devices

The rights of children laid down in the United Nations Convention on the Rights of the Child¹⁸ (and adopted by the EU member states) need to be fully respected, and in particular, the right to make the best interest of the child a primary consideration (article 3) and the right of the child to enjoy the highest attainable standard of health (article 24). The goal of documenting clinical performance and safety of high-risk medical devices as best as feasible must be achieved along with the goal of not excluding vulnerable paediatric patients from receiving state-of-the-art medical treatment, including the use of medical devices, based on current knowledge, technology and innovation.

The EU MDR addresses the ethical aspects of the clinical investigation of medical devices in minors, including scientific justification for clinical investigation, procedures of obtaining informed consent of legally designated representatives and involvement of minors themselves in this process.¹ In accordance with the EU MDR and the FDA draft guidance on ethical consideration for clinical investigations of medical products in children,¹⁹ the experts emphasised that children, as a vulnerable population, are entitled to additional safeguards. With respect to the ethics review, following FDA guidance, the panel agreed on the critical importance of the following aspects. First, the expected risks and benefits associated with the use of the medical device that is subject of a proposed clinical investigation

need to be assessed up front. Distinct clinical characteristics of the paediatric population to be studied, type of device and duration of its use, and potential effects of the intervention on child growth, development and overall health should be taken into account. Second, the scientific necessity of conducting a clinical investigation in children needs to be evaluated and be balanced with the potential burden and risks imposed on studied paediatric patients, especially in cases where data on device performance and safety in adults is already available. In such cases, extrapolation of data obtained from trials exclusively in adults can be considered for devices with the same intended use in children, particularly if the condition treated is similar in children and adults and if there is no indication for differences in effectiveness and safety of the device in children and adults. Similarly, mixed population studies involving both adults and children can be considered in order to optimise sample sizes and for best use of resources in case of shared indications for device use between the groups.^{19,20} Finally, the protocol for a proposed clinical investigation involving children needs to be assessed in order to ensure that only well-designed studies are conducted, devoting particular attention to the choice of relevant outcome data and potential control group.

4.6 | Required clinical evidence on high-risk medical devices in children

For high-risk medical devices established on the market for several years with a history of apparently safe use, certification under MDR should be made possible after an evaluation of existing clinical evidence by a notified body. If necessary (when evidence is limited) also recommendations from competent paediatric experts should be obtained. The certificate of conformity could then be granted with conditions that might include a requirement for additional post-marketing surveillance, such as the use of registries and clinical follow-up studies. For novel high-risk medical devices for children, the requirements for clinical investigation supporting evaluation and market access should be decided upon by competent panels with involvement of experienced paediatricians on a case-by-case basis.

In line with the FDA guidance on the premarket assessment of paediatric medical devices, the experts agreed that there is no common approach that would be appropriate for all medical devices intended for paediatric patients.²⁰ Different levels of clinical evidence are required depending on the specific research question addressed, the type of device, the identification of potential hazards and expected risks associated with its use, the nature of the conditions to be treated with the device, the prevalence of these conditions and the intended age group for use.

RCTs are the gold standard for evaluating the therapeutic benefits of medical interventions and should be performed whenever feasible. In the paediatric age group, RCTs may be feasible in common conditions with a large number of affected paediatric patients, in non-urgent interventions, and in older children and adolescents.

An example could be the comparison of a novel method of continuous glucose monitoring in diabetic children with a conventional approach. Double blinding in RCTs on medical devices may often be difficult to achieve and open RCTs, with design elements to reduce risk of bias other than blinding, can be informative.

For ethical reasons, RCTs can only be performed if there is equipoise between the tested intervention and an available control or no intervention, meaning that there is no clear indication for superiority or inferiority of the tested intervention compared to the control arm. Under most conditions of testing medical devices in children this is not the case, and thus performing an RCT would not be ethical.

For many medical devices used in children, RCTs are not feasible because, for example only a small number of patients are available, events are rare, or populations are very heterogeneous. Therefore, while aiming for the highest level of evidence possible, other study designs need to be considered to generate clinical data on device performance, effectiveness and safety. In general, the established hierarchy of evidence should be followed as categorised²¹:

1. RCT (the highest level of evidence)
2. Comparative prospective study with concurrent controls (experimental or observational)
3. Comparative study without concurrent controls (for example with historical control)
4. Prospective case series with documentation of either post-test or pre-test/post-test outcomes

A paediatric expert panel should decide on case-by-case basis which of these levels of evidence would need to be met for evaluation of a specific device and accept documentation of retrospective case series as suitable clinical evidence only in exceptional cases when alternative options cannot be achieved, previous experience with the device in children or adults exists, and there is an urgent medical need for the device. In addition to clinical data, technical specifications, pre-clinical data such as results of in vitro testing and animal studies, and expert opinions may provide informative data complementing limited clinical evidence. In such cases, special emphasis should be put on continued data collection and monitoring after market introduction.

In the interest of patient safety, both pre-clinical and clinical evidence should be made publicly available. The MDR requires to publish a report for all clinical investigations authorised under MDR in the European Database on Medical Devices (EUDAMED), which is currently under development.

4.7 | Post-marketing surveillance

To enable meaningful post-marketing surveillance, European patient registries need to be established that include children treated with medical devices. Data on the patient and disease characteristics, the conditions of the device use and immediate

and long-term patient outcomes should be entered in standardised fashion. Generally, a longer-term follow-up should be achieved given that medical interventions in childhood can have a lasting impact on later health. Such registries should be supervised by European paediatric and/or rare disease patient associations. The data should be regularly monitored and interpreted with competent paediatric experts. The building of such European registries could capitalise on the knowledge, experience and infrastructure of established national registries and European Reference Networks. Long-term funding of such registries needs to be secured, for example by contributions from manufacturers and healthcare facilities, based on a set fee per device used, and public co-funding given that there is a public interest in generating these data even in situations of no commercial profitability.

4.8 | Consensus recommendations summary and conclusions

The workshop participants agreed upon selected key aspects of clinical evaluation of high-risk medical devices in children and formulated their recommendations accordingly, as shown in [Box 1](#). The need for establishing a paediatric expert panel with respect to paediatric medical devices, transparency of clinical evidence supporting medical device evaluation and certification, and for agreement

BOX 1 Summary of the consensus recommendations on the selected aspects of clinical evaluation of high-risk medical devices in children.

Consensus recommendations on aspects of Clinical Evaluation of High-risk Medical Devices for Children

- An expert panel with respect to paediatric medical devices and with the involvement of paediatric experts should be established to provide scientific and clinical advice:
 - to developers of new and high-risk medical devices in accordance with MDR Article 61(2).¹
 - to the Medical Devices Coordination Group with respect to the consistent application of the MDR on medical devices used for children in accordance with Article 106 of the MDR.
- Notified bodies who certify paediatric medical devices should be required to seek advice from competent paediatric experts.
- Transparency is necessary regarding:
 - the advice of expert panels concerning clinical evidence expectations provided to device developers in accordance with Article 61(2),
 - the clinical data relied upon by manufacturers for paediatric medical devices to ensure that developers can predict clinical evidence requirements, and healthcare practitioners have access to the often limited clinical data relating to the device.
- Designation of an orphan medical device status should be based on a case-by-case evaluation, taking the following criteria into account:
 - Intended use in a life-threatening or chronically debilitating disease with a prevalence of <1 per 2000 people, based on the accepted definition of rare diseases in the EU,¹⁶
 - Existence of an unmet medical need and
 - Absence or insufficiency of suitable or equivalent alternative therapeutic options with similar clinical safety.

BOX 2 Summary of the consensus recommendations on the approach to clinical investigation of high-risk medical devices in children.

Consensus Recommendations on Clinical Investigation of High-risk Medical Devices for Children

- No common, generic approach to clinical investigation of all medical devices intended for paediatric patients can be applied.
- Different levels of clinical evidence are required depending on the specific research question addressed, the type of device, the identification of potential hazards and expected risks associated with its use, the nature of the conditions to be treated with the device, the prevalence of these conditions and the intended age group for use.
- The approach to clinical investigation of medical devices in children should consider:
 - RCTs are the gold standard for evaluating therapeutic benefits of medical interventions and should be performed whenever feasible.
 - For most medical devices used in children, RCTs are not feasible for ethical or practicality reasons, hence other study designs need to be considered to generate clinical data on device performance and safety. Generally, one should strive for the highest level of clinical evidence that is achievable, categorised as²¹:
 1. RCT (the highest level of evidence)
 2. Comparative prospective study with concurrent controls (experimental or observational)
 3. Comparative study without concurrent controls (e.g. with historical control)
 4. Prospective case series with documentation of either post-test or pre-test/post-test outcomes
- Mixed population studies involving both adults and children can optimise sample sizes and best use of resources in case of a shared indication for device use and should include age-based subgroup analyses.
- Extrapolation of data obtained from trials in adults can be considered for devices with the same intended use in children, if the condition being treated is similar and if there is no indication for different effectiveness and safety of the device in children.
- For post-marketing surveillance, European patient registries should be established and supervised by competent paediatric associations that systematically collect relevant and informative data on paediatric patients treated with medical devices of interest.

on criteria regarding designation of an orphan medical device status were emphasised. With respect to clinical investigation, key recommendations were developed, as summarised in [Box 2](#). These focused on the context-tailored approaches to clinical investigation of high-risk medical devices in children taking into account the feasibility of obtaining clinical evidence of the highest level given ethical and practical considerations.

The workshop participants and the CORE-MD consortium members offered to contribute to the development of concepts and practical approaches for evaluating high-risk medical devices, including approaches for clinical investigation, within the existing legal framework of the EU. They also offered to identify further individuals with expertise on the use of implantable and class III medical devices in children and/or on regulatory processes in relation to children, who could contribute to Expert Panels.

The clinical experts agreed to work together with paediatric associations across Europe to increase awareness on the consequences of the EU MDR and its implementation for the medical care of sick children arising from the increasing unavailability of essential medical devices for paediatric patients. This joint activity should also call for politicians and policymakers to review the existing EU legal framework, to ensure effective protection of the rights of children in the EU.

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CONFLICT OF INTEREST STATEMENT

UB received financial support from Albireo, Alexion, Mirum, Nestle, Vivet. AE is a proctor for Medtronic and a consultant for Lifetech, Gore. DK is a proctor for Venus Medtech, Edwards Lifesciences, Medtronic and Occlutech. TM has acted as unpaid advisory board member of Pumpinheart Ltd., and previously as senior medical officer in medical devices at the Health Products Regulatory Authority, Ireland and previous co-chair of the Clinical Investigation and Evaluation Working Group of the European Commission. OM received financial support from ASENSUS Surgical, Corza, Aesculap AG, and Hollister/Dansac Academy. The other authors declare no potential conflict of interest in relation to the content of this manuscript.

DISCLAIMERS

AHJ: The views expressed in this article are the personal views of the author and may not be understood as being made on behalf of the employer/organisation. GMG: The contributions from the author were advisory in nature, by providing regulatory information and context, and were independent to the consensus recommendations in this article. PP: The information and views set out in this article are those of the author and do not necessarily reflect the official opinion of the European Commission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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