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Clinical trials in children

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Safety and efficacy data on many medicines used in children are surprisingly scarce. As a result children are sometimes given ineffective medicines or medicines with unknown harmful side effects. Better and more relevant clinical trials in children are needed to increase our knowledge of the effects of medicines and to prevent the delayed or non-use of beneficial therapies. Clinical trials provide reliable evidence of treatment effects by rigorous controlled testing of interventions on human subjects. Paediatric trials are more challenging to conduct than trials in adults because of the paucity of funding, uniqueness of children and particular ethical concerns. Although current regulations and initiatives are improving the scope, quantity and quality of trials in children, there are still deficiencies that need to be addressed to accelerate radically equitable access to evidence-based therapies in children.

Imperative to conduct trials in children

Since the acknowledgement of children as 'therapeutic or pharmaceutical orphans' in the 1960s [1–3] there has been a worldwide recognition of the need to conduct trials of medicines used in children as a mechanism to improve the health of children [4–7]. Significant advances in child health have resulted from the conduct of paediatric trials. Well-known trials of polio vaccines and the subsequent rapid translation into practice were instrumental in the successful and almost complete eradication of polio [8, 9]. Recent advances in multicentre cancer trials in children have increased childhood cancer 5 year survival from 28% in the late 1960s to 79% by 2005 [10–13]. Regrettably, these stories of remarkable benefits cannot be extended to many other childhood conditions [14] because of the dearth of relevant trials.

Prescribing in children is often based on extrapolation from trials in adults due to the lack of paediatric data. Children are not 'little adults,' but are a heterogeneous group, ranging from preterm neonates to post-pubertal adolescents [15–17]. Their disease presentation may have a different natural history from adults and they may also suffer from diseases which do not occur in adults [18–20]. Children have complex physiological, developmental, psychological and pharmacological characteristics that vary from adults and these features are also different across the newborn to adolescent age range [21]. They may metabolize certain medicines differently from adults resulting in sub-optimal therapy, unexpected responses, adverse drug reactions and toxicity which may affect development and future reproductive capacity [22–24].

Relying on adult safety and efficacy data when prescribing in children can have unpredictable and tragic effects [4, 17, 25]. For example, faster metabolism of cyclosporin in children could lead to subtherapeutic concentrations because of under-dosing [26]. Prescribing tetracycline in children during the period of mineralization of developing teeth results in severe enamel dysplasia [27]. Children may experience paradoxical hyperactivity with phenobarbital which is not experienced in adults due to differences in pharmacodynamics [26]. In neonates, because of the immaturity of the liver, reduced medicine clearance resulted in the Gray baby syndrome with chloramphenicol [28, 29], hepatotoxicity, hypotension, renal

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failure and death with the solvent propylene glycol which was in E-Ferol® [30] and 'gasping syndrome' from metabolic acidosis with formulations containing benzyl alcohol [15]. Thalidomide was used for morning sickness in pregnant women with devastating effects on foetal development, resulting in thousands of children being born with phocomelia [31].

More trials are needed, especially in areas of high clinical need. A study in 2007 showed that the number of randomized controlled trials in adults published in five high impact general medical journals has nearly doubled over 20 years, while the number of paediatric trials has not increased [32]. Despite about 27% of the world's population being children [33], paediatric trials constitute only 16.7% of the total number of trials registered on the World Health Organization (WHO) portal [34]. In a study of trials registered on clinicaltrials.gov on selected medical conditions, only 12% were paediatric trials although children contributed to almost 60% of the total disease burden [35]. The WHO Global Burden of Disease study in 2002 estimated 11.4 million deaths in children under 10 years of age with 91% of these in children less than 5 years [36]. Fewer trials are conducted in younger children where they are most needed [37]. Only 7% (42) of all paediatric trials published in 2007 were in neonates [38, 39]. There are a disproportionately small number of trials in children in low income countries [40, 41]. Over 89% of children live in low and lower to middle income countries, but only about a quarter of the 604 trials of medicinal products in children published in 2007 were conducted in these countries [38].

The pharmaceutical industry funds a greater proportion of trials in adults (65%) than children [35, 42]. Industry may be reluctant to conduct trials in children due to decreased commercial interest, increased cost and greater risk of liability [20, 43–45]. The more restrictive regulatory oversight for paediatric trials [23, 46] which includes the recommendation for provision of medicines post-trial to participants where there is proven therapeutic benefit [47, 48], may further discourage industry from conducting trials in children. Funding for paediatric trials therefore often relies on non-profit organizations, which have limited funding. The government favours trials in adults because of political and economic pressures [17, 35].

Study design and conduct of paediatric trials

There are special considerations when designing any of the four phases of clinical trials in children [49, 50]. Phase I trials, which test the safety and pharmacokinetics of a new intervention for the first time, are discouraged in children due to the unknown effects of the intervention [51, 52]. However, phase I trials are more acceptable in children with severe or life-threatening conditions where there is no proven treatment or when standard therapies have failed [51, 52]. Phase I trials can only occur when there are appropriate pre-clinical safety and efficacy data available from animal studies, modelling or other predictive studies [53]. Phase II trials, which study the safety and efficacy of the intervention [51], are sometimes conducted in children. Generally medicinal product testing in children is deferred until the trials reach phase III which evaluates efficacy, acceptability and adverse effects [54]. Although the intent of the deferral is to protect children from exposure to unnecessary harm, it also means a delay to the access of children to potentially useful medications [54]. Phase III trials (randomized controlled trials) compare the investigational intervention with standard therapy, another effective therapy or placebo to estimate unbiased treatment effects [54–56]. Control groups and placebos are used when there are no established alternative therapies [54, 57–59]. Phase IV post-marketing trials are infrequently conducted in children. However, the Food and Drug Administration (FDA) Paediatric Research Equity Act (PREA) requires paediatric trials of marketed medicines [60].

Pharmacokinetic studies

Pharmacokinetic studies (which generally occur in phase I) are important in the different paediatric age ranges. Challenges with pharmacokinetic studies include the lack of expertise in paediatric population pharmacokinetic or pharmacodynamic analysis, problems associated with the number, volume and timing of sampling and the absence of sensitive micro-analytical techniques to determine accurately the drug concentration of very small volume specimens [61]. If the disease progression is similar between children and adults, an initial dose extrapolated from adult data may be adequate, followed by pharmacokinetic studies to determine the most appropriate paediatric dose [62]. Another approach is to conduct single dose paediatric studies in the different age groups if medicines are known to have linear pharmacokinetics in adults [63]. In paediatric pharmacokinetic studies, innovative trial design techniques for reducing the number and volume of samples required are sometimes used. These techniques use sparse and scavenged pharmacokinetic samples with population pharmacokinetic methods using non-linear mixed effects [61, 63]. Opportunistic trials, which collect pharmacokinetic samples from children receiving treatment as part of routine clinical care, is another low risk and high yield design that is efficient and acceptable to parents and ethics committees [61]. Pharmacogenomics methods are also being developed for investigating drug disposition, efficacy and safety [46].

Trial registration and publication

Public registration of clinical trials is especially important to protect participants from unnecessary, duplicative studies, to improve transparency and overcome publication and selective outcome reporting bias [37, 64–66].

Prospective registration of trials is strongly advocated internationally by regulatory authorities, ethics committees and journals as a condition of publication [67]. However, a review of published paediatric randomized controlled trials showed that some were poorly reported [42] and had incomplete reporting of adverse drug reactions [68]. Disappointingly a considerable number of paediatric trials that were conducted as a result of the paediatric exclusivity legislations were not published [69]. For paediatric trial results to be translated into clinical practice, prompt and accessible publication of unbiased results including negative results helps to improve public trust and confidence in paediatric research [70–72].

Small trials sizes for paediatrics

The recruitment of children in trials is more difficult than for adults [45, 47] because of the lower burden of disease in children [46, 73, 74]. Most paediatric trials have small sample sizes [35, 38, 41] with only 38% of 736 paediatric trials published from 1996 to 2002 having a sample of more than 100 [40]. The small sample size, heterogeneity of response of children to treatments and rarity of certain important outcomes contribute to the problem of inadequate power [75]. Underpowered trials may provide inconclusive results and fail to detect modest but clinically relevant outcomes including adverse effects [17, 21, 55, 71]. This may waste resources and the efforts of children's participation in trials [76]. To address the small sample sizes in children, there have been major achievements in developing statistical methods and collaborative specialist multi-national groups and paediatric clinical trials networks that pool their data and resources [77–82].

Attitudes to participation in trials

There has been a general reluctance about involving children in trials particularly by parents and doctors because of fears of harming children by exposing them to uncertain treatment effects [45, 72, 83]. In particular, parents were anxious about their child being treated as a 'guinea pig' and were concerned that investigators may have conflicting interest and do not have their child's health as a priority [45, 84]. However, in a neonatal study 75% of parents believed that their doctor would not approach them to do research if it might place babies in real danger and 50% reported that they trusted their doctor and would agree to participate in a trial if suggested by their doctor [85]. Practitioners interviewed in a study in 2011 were apprehensive and averse to recruiting children for trials due to the trial burdens which included the overwhelming amount of information they had to provide to the families [72]. Assisting practitioners to understand families' perceptions of trials and providing 'moral' support may improve recruitment of children [72]. In contrast, parents who reported a positive recruitment experience, viewed participation in a trial as an 'exciting' opportunity, felt a sense of comfort and safety, acknowledged the value of research and desired to be informed about a trial if their child was eligible [72]. Other positive aspects parents experience include the altruistic desire to help future children, the opportunity to access new therapies, increased access to health care professionals and medical information, better medical care for their child, meeting other parents in a similar situation and feeling a sense of hope when no other effective therapies are available [72–74, 86, 87]. The high level of threat and need for hope may account for the generally high rates of recruitment to neonatology and childhood cancer trials [83]. There are also perceived benefits for children participating in trials. Children often enjoy being part of a trial, interacting with other participants, being able to contribute to helping other children and are empowered about their treatment [84].

There has been some work on developing strategies to aid parents in the decision making process for trial participation [88]. Some strategies include improving the readability of the consent [89]. Masty *et al*. conceptualized a 'goodness-of-fit' approach to informed consent for paediatric trials that encouraged investigators to create consent procedures that took into account the research context, the child's cognitive and emotional maturity and the family system [90]. The James Lind Library has been created to help the public understand that trials are fair tests of treatments in health care [91].

The use of placebo is poorly understood by parents who do not understand the rationale for using placebo to determine whether the intervention is effective or necessary. Parents fear assignment of their child to the placebo arm or to the treatment arm which is later proven to be less effective [45, 92, 93]. This concern may be compensated for by providing the proven effective treatment to all participants at the conclusion of the study. Alternative randomization methods should also be considered which may be more acceptable to parents. In a conventionally randomized trial, parent's views were evenly divided on accepting the controversial Zelen randomization where randomization occurs prior to discussion with the family and only if the child is allocated the experimental treatment arm is consent sought [94]. In a survey investigating different types of consent to hypothetical neonatal resuscitation trials, parents wished to be responsible for making the informed decisions and were more comfortable with prospective consent than deferrals, waivers or 'opt-out' options [95].

The burdens of trial participation for children are different from adults. For example children's aversion to needles makes obtaining blood samples challenging. To address this burden and protect children from unnecessary testing, the volume of blood sampling generally allowed in paediatric trials is less than 3% of the estimated circulating blood volume over a 2 to 8 week period [20, 96, 97]. Alternative appropriate sampling techniques, for example finger or heel pricks or salivary samples, may be preferred as they minimize discomfort for children [15, 20, 96, 97].

There is a strong advocacy that paediatric trials require the same dedicated time and attention to educate families and participants ensuring an appropriate child friendly environment and adapting treatments to their special needs that is generally accepted as routine clinical care [98, 99]. The use of pragmatic trials where there are no additional burdens of testing and monitoring beyond the requirements of routine clinical care [37–40] may also alleviate some of these concerns, including the use of placebos [55]. Participation may also be improved by having trained investigators who understand the complexities of conducting trials in children, appropriate facilities that meet the needs of children and a designated trials co-ordinator to facilitate recruitment and trial conduct [45, 93, 100]. Increasingly the importance of engaging children and families in the recruitment, consent and design of trials has also been recognized [99].

Appropriate medicine formulations in trials

The development of appropriate formulations for children has been slow. This may be due to historical disasters such as the formulation of sulphanilamide as an elixir which used diethylene glycol without animal toxicity testing resulting in poisoning and deaths in the 1930s [101, 102]. Consequently, risk averse companies may be reluctant to develop paediatric formulations due to the potential harmful effects of excipients used in the products and the low market share of these products. To encourage the pharmaceutical industry to develop paediatric appropriate formulations, the 2003 FDA Best Pharmaceuticals for Children Act (BPCA) [103] and European Union Paediatric regulations were endorsed.

Administration of medicines in children is complex and the trial design needs to consider the child's developmental abilities and the medicine's acceptability and tolerability as this will impact on compliance. Children are fearful of injectable medicines and if an alternative route of administration is not available, the provision of local anaesthetic gels or patches will decrease discomfort. The requirements of child friendly formulations may differ in resource limited settings where there may be a lack of refrigeration facilities which may impact on the stability and efficacy of the medicine [104]. When there is a lack of paediatric appropriate formulations, the use of adult dose forms such as tablets and capsules can be problematic for younger children who cannot swallow tablets as crushing tablets or opening capsules and dispersing in liquids may compromise the palatability and bioavailability of the medicine and affect the trial results [96]. The inclusion of extemporaneous preparation guidelines in paediatric trials which use solid oral dosage forms, will improve the accuracy and reproducibility of the preparation [73]. Skin patches or flexible oral solid dosage forms such as dispersible tablets or powders, melts (wafers, sublingual) and sprinkles may be more suitable across various settings [102].

Outcome measures

As children grow and mature through the developmental stages, it may not be suitable to use the same outcome measures when comparing children of different ages and stages [16]. Some outcomes such as pain, nausea, dizziness, level of sedation or visual and auditory responses [42] are difficult to measure and report in young children. When designing how to measure these outcomes, researchers need to consider using age-appropriate tools such as the face pain scale [57, 105]. Because of differences in body composition in different age groups, pharmacokinetic studies have sometimes resulted in incomplete and incorrect conclusions [96]. Trials that include different paediatric ages may need appropriate dose adjustments by weight or body surface area [96, 106]. Researchers are increasingly recognizing the importance of qualitative outcome measures that are relevant to the child and family, including the impact of the illness and treatment on the quality of life [16]. When measuring quality of life outcomes consideration needs to be given about whether to use proxy response by parents or reporting by the child or both [107], as these may differ. Involving parents and children in the selection of outcome measures that are important to them is recommended [16, 21].

Ethics of paediatric clinical trials

There is a dilemma in finding a balance between the obligation to conduct trials to protect children from the risk of using untested medicines and to protect children against unknown risks and harms which may occur with trial participation [27, 39, 108, 109]. The ethical principles of respect for persons, beneficence, non-maleficence and justice in trials involving children are the same as for adults. There are additional ethical challenges because children lack the capacity to understand the risks involved in trials and depend upon adults to make decisions for them [110]. In a review of 739 paediatric trials from 1996 to 2002, 523 (71%) reported adverse drug reactions, but only 13 (2%) of the trials had safety monitoring committees [4]. Since then, trial governance is becoming more stringent with a requirement for an independent safety monitoring board with paediatric expertise, who can appreciate the uniqueness and unpredictability of responses in children [76, 111]. Long term follow up in children is particularly important as many adverse effects may present later in life [17, 44].

Informed consent and assent

Informed consent for participation in paediatric trials is more complex than adult studies because consent is by proxy from the parents or guardian, who have a duty to protect the child's welfare [112]. Parents are uncomfortable with this responsibility because they are making a

decision for their child [87]. Mason & Allmark propose that parents' consent in trials is vital to socially recognise parental roles, but does not offer added protection for neonates to that provided by appropriate research ethics, safety monitoring and governance procedures and parent's knowledge of these measures would improve decision making [113]. A review by Shilling & Young indicated that parents are keen to take responsibility for the decision to enrol their child in a trial, but are also fearful of making the 'wrong' decision' [83]. They also reported that individual parent's understanding of the threat of the child's condition and the trial risks depends on their personal values and experiences, their child's medical condition and the type of the trial [83]. Suggestions to address some of these parental concerns identified in this review include positive interactions at recruitment with the flexibility to tailor discussions to the needs and circumstances of individual parents [83]. The study by Woolfall *et al*. in 2013 suggest that the investigating team involved in recruitment need to be aware of parents' priorities and the sorts of misunderstandings that can arise with parents [86]. A goodness-of-fit approach is described by Masty & Fisher whereby consent procedures are tailored to the research, the cognitive and emotional maturity of the child, the family system, the participants' priorities and well-being and are focussed on the issues that are of concern to potential participants and helping them achieve understanding of a trial [90]. To improve recruitment of children the study by Woolfall *et al*. also recommended providing tailored trial information on aspects that parents considered important in making a decision for their child participating in a trial [86]. Also information about the trial should be provided not only to parents but also to children in an age-appropriate method to improve comprehension, show respect, preserve trust and enable co-operation [98, 114]. The most frequently cited suggestions from interviews and focus groups for improving informed consent related to allowing parents more time to make their decision, the amount and type of information provided, organization of the consent meeting, communication style and providing additional materials [115]. Although consent by parents or guardians is a legal requirement for trials, the autonomy of children should be respected and investigators also need to include them in decision making as much as they are capable [27, 87, 116]. Children's dissent should also be respected, particularly if their dissent is different from their usual response to the same procedure in normal clinical care.

Payment for participation

Although it is common practice to compensate trial participants for travel, parking, meal allowance and accommodation [54], payments for participation in trials is more controversial in children [117]. The types of payment can be in the form of *reimbursement* for direct trial-related expenses, *compensation* for the time and inconvenience of trial participation, *appreciation* after participation to thank them for their involvement and *incentives* to reward enrolment above actual out-of-pocket expenses [112, 117]. While the European Union (EU) advocates banning of all incentive payments to children [118], this is common practice in the United States (US) where almost 25% of paediatric trials offer payment [117]. The ethical concern about large incentive payments is that it might entice and distort the judgement and decision of the parent or child about the risks of trial participation [112, 118]. However, non-payment for direct expenses and inconvenience of trial participation may create unnecessary financial obstacles for participation and risks hindering essential paediatric research [45, 117–119]. The ethics committees, investigators and sponsors need to ensure that payment for trial participation of children is fair by keeping payments reasonable [98, 120].

Advocacy for trials

The 1989 'Convention on the Rights of the Child' 'recognizes the right of the child to the enjoyment of the highest attainable standard of health' [121]. This includes the right to have research evidence for treatments commonly used in children. It is a reasonable requirement for the developmental pipeline of new interventions to include children in trials when use in children is anticipated [55, 122]. Several rigorous guidelines including the Belmont Report [123], Declaration of Ottawa on Child Health [124], Declaration of Helsinki and International Conference on Harmonization (ICH) E11 [15, 125] address the need for paediatric trials and protection of the rights and welfare of children. Many countries have also developed their own regulations, guidelines and standards for the inclusion of children in trials [22, 54, 57, 126–128].

Paediatric legislations

Most medicines used by children internationally are unlicensed or off-label, with no randomized controlled trial data in more than 50% of interventions used in children as compared with adults [44, 71, 129–131]. The US was the first to initiate legislative changes in 1997 to encourage more trials in children to improve the evidence base for medicines in children [28, 51], followed by the EU in 2007 [7, 132–135] (Figure 1). Their expectations were for the pharmaceutical industry to evaluate the safety and efficacy of medicines used by children in all appropriate paediatric age groups, to ensure that product labels contain the known paediatric data, to develop paediatric appropriate formulations and to provide a Paediatric Investigation Plan for testing in children at the time of medicine application submission [122]. Both regulations have mandatory requirements with an incentive of a 6 month extension of patent protection to encourage the pharmaceutical industry to conduct paediatric trials. These incentives resulted in

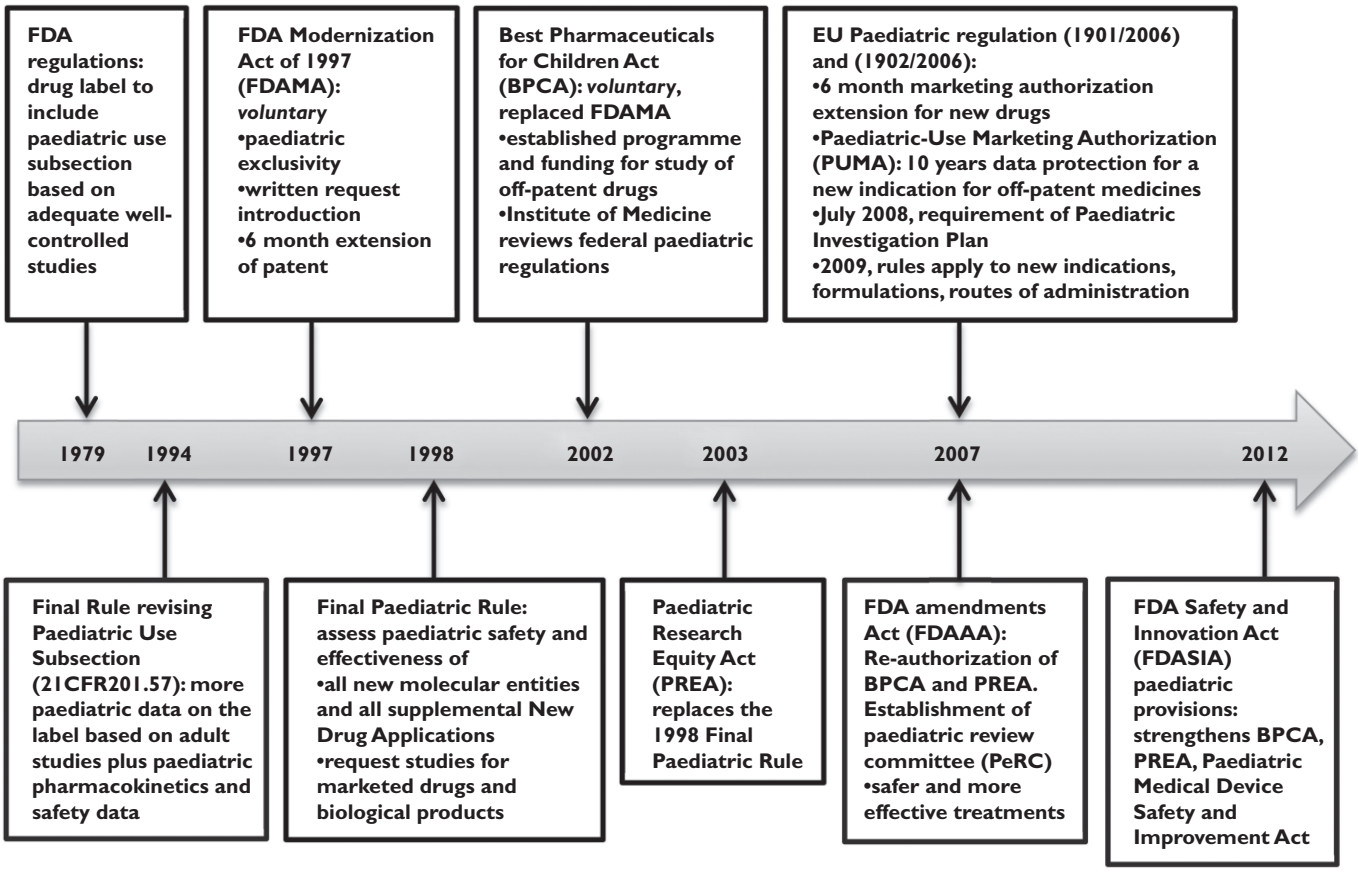

Figure 1
Timeline of paediatric regulations in the US and EU

an increase in the number of in paediatric trials [136–138]. By March 2008, more than 49 000 children were enrolled in trials and the FDA had granted exclusivity to 150 medicines and granted requests for 842 studies which were mostly for new indications of existing medicines [134]. The FDA 'New Paediatric Labelling Information Database' provides information of new paediatric trials that resulted in new or enhanced safety data in children [137, 139]. In a retrospective analysis of the applications for Paediatric Investigation Plan and Waivers submitted to the European Medicines Agency (EMA), from 2007 to 2009, there has only been a slight increase in the proportion of paediatric trials from 8.2% of all trials in 2007 to 9.4% in 2009 [140]. The main therapeutic areas of applications were endocrinology (13.4%), oncology (11%), infectious diseases (10.8%) and cardiovascular diseases (7.1%) [140]. This pattern reflected the commercial interest of the pharmaceutical industry to evaluate medicines with a high market value and which are commonly prescribed in adults rather than addressing the priority health needs of children [140, 141]. Many frequently prescribed, essential medicines that are off-patent and have a small market share in children have yet to be investigated [39, 142, 143]. This is because incentives for the development of off-patent medicines in both the US and EU are small and voluntary and public funding is inadequate [142].

The pharmaceutical industry does not appear to be interested in transferring the benefits of approved paediatric appropriate medicines in the US and EU to other countries. This may be due to the lack of economic incentives and the high costs associated with amending the labels of existing medicines with new paediatric data or registering new medicines. Therefore, there needs to be an efficient, harmonized process globally through collaboration of government, pharmaceutical industry and the medical community to ensure that the development of paediatric medicine is optimally aligned with priority health care needs [45, 142]. Canada and Japan have implemented modest paediatric regulation reforms [142]. Other countries need to adopt regulations and incentives for promoting paediatric medicines research with sustained government and societal support.

International paediatric trials initiatives

Global priorities of the WHO Millennium Development Goals include the 'Make medicines child size' initiative and

the World Health Assembly "Better Medicines for Children" Resolution WHA60.20 in 2007 to improve knowledge, access, research and development of paediatric medicines [144, 145]. Another WHO initiative is the Paediatric medicines Regulator's Network (PmRN), which involves National Medicines Regulatory Authorities (NMRAs) which aim to harmonize the regulation of manufacture, license and research of medicines for children [144].

International paediatric trial networks have been established in many countries to address some of the challenges by improving the infrastructure and research capacity. The US and EU created networks with specialized expertise in conducting trials in children and have dedicated funding for paediatric research and training [142]. The US National Institute of Child Health and Human Development (NICHD) Pediatric Trial Network (PTN) was launched in September 2010 with US $95 million for 7 years to conduct paediatric trials on off-patent medicines [146]. This network provides an appropriate environment for performing safe and effective trials in children as recommended by the Best Pharmaceuticals for Children Act (BPCA) drug development programme in a variety of therapeutic areas [146]. In 2012 the network, in collaboration with the FDA, has commenced paediatric studies on 30 drugs [147].

The Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)] was established in March 2011 in collaboration with research networks, investigators and centres with recognized expertise in conducting paediatric trials [148]. This network is working towards developing the necessary competences and avoiding unnecessary duplication of paediatric studies, educating parents or carers and children about trials and encouraging their participation, raising awareness among health care professionals of the necessity for trials in children of all ages, supporting their involvement in such studies and engaging in dialogue with ethics committees on paediatric trials issues [148]. The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) in the UK was established in 2005. This network has been more successful because of funding from the government [99]. The Standards for Research in (StaR) Child Health is an international initiative founded in 2009 to improve the quality of the design, conduct and reporting of paediatric trials by promoting the use of internationally developed research standards to enhance their reliability and relevance [5, 149–151].

Professional bodies and research organizations internationally have also recognized the imperative to conduct paediatric trials. These include the International Paediatric Association (IPA [152]), the American National Institute of Health (NIH) [153, 154] and Academy of Paediatrics (AAP) [54], the UK Medical Research Council (MRC) [155] and Royal College of Paediatrics and Child Health (RCPCH) [156] and the European Agency for the Evaluation of Medicinal Products (EMEA) [125].

International collaborative disease specific groups have been formed to address the logistical and methodological difficulties in conducting trials of diseases with a low prevalence [80]. Examples of successful disease specific groups include the Children's Oncology Group (COG [77]), Paediatric Rheumatology International Trials Organization (PRINTO) [79] and Paediatric European Network for the Treatment of AIDS (PENTA [81]). As a result of collaboration, the Children's Oncology Group has developed a research culture in the participating institutions which accepts protocol-driven trials as part of standard care [13]. It has also facilitated rigorous protocol development and review, centralization of pathology review, central database and safety monitoring of toxicity and response, internal auditing to ensure compliance to Good Clinical Practice and involvement of established investigators with oncology paediatric expertise [45, 157]. PRINTO has a Scientific Advisory Council, International and National Coordinating Centres to facilitate logistics and scientific elements of multicentre, multinational studies [80]. PRINTO's achievements include developing standardized treatment outcome measures, training young researchers, access to network facilities for the conduct of trials and establishing a website for families to access health information [80]. All these global initiatives can be adopted by other disease specific groups to support the collaborative efforts to increase the number of clinically relevant paediatric trials.

The way forward

Although progress has been slow, paediatric clinical trials have undergone a renaissance with international recognition of the importance of trials in children. However, there continue to be deficiencies including inadequate funding and conflicts of interest with trials still being driven by financial and political incentives. Health policy makers need to consider the needs of children by setting priorities, developing infrastructure and providing sufficient funding [158] that is sustainable to accelerate the progress of equitable health care. The future health of children hinges on the success of paediatric trials. Greater advocacy and collaboration between all major stakeholders including regulatory authorities, pharmaceutical industries, scientific community, clinicians and the public at the national and international level is crucial to this success. Investment into better evidence-based treatments for our children is an investment into a better future for all.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

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