

Clinical trials in children

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The imperative to undertake randomised trials in children arises from extraordinary advances in basic biomedical sciences, needing a matching commitment to translational research if child health is to reap the benefits from this new knowledge. Unfortunately, many prescribed treatments for children have not been adequately tested in children, sometimes resulting in harmful treatments being given and beneficial treatments being withheld. Government, industry, funding agencies, and clinicians are responsible for research priorities being adult-focused because of the greater burden of disease in adults, coupled with financial and marketing considerations. This bias has meant that the equal rights of children to participate in trials has not always been recognised. This is changing, however, as the need for clinical trials in children has been increasingly recognised by the scientific community and broader public, leading to new legislation in some countries making trials of interventions mandatory in children as well as adults before drug approval is given. Trials in children are more challenging than those in adults. The pool of eligible children entering trials is often small because many conditions are uncommon in children, and the threshold for gaining consent is often higher and more complex because parents have to make decisions about trial participation on behalf of their child. Uncertain about what is best, despite supporting the notion of trials in principle, parents and paediatricians generally opt for the new intervention or for standard care rather than trial participation. In this review, we explore issues relating to trial participation for children and suggest some strategies for improving the conduct of clinical trials involving children.

The importance of clinical trials in children

Clinical trials in children have resulted in significant improvements in their health care. A well-known example is childhood acute lymphoblastic leukaemia, in which the 5-year survival improved from 25% to more than 70% as a result of multicentre trials.¹ Unfortunately, since there are few paediatric trials,² the list of improvements in child health resulting from clinical trials is not long and is restricted to some childhood diseases, heavily clustering around cancer. Consequently, many ineffective and even harmful interventions are used in children before they have been appropriately assessed in randomised trials,^{3,4} and other useful interventions have had a delayed introduction into practice. In the absence of specific trial-based data in children, clinicians, families and policy-makers are forced to extrapolate from results of studies in adults. This extrapolation is often inappropriate because children have a different range of diseases, and metabolise medications differently, resulting in responses to treatment that are unpredictably different to adults.^{2,5,6} For example, the adverse effects to medications such as thalidomide (phocomelia in the unborn child), tetracycline (staining of the teeth), chloramphenicol (the grey baby syndrome), and aspirin (Reye's syndrome in children with viral infections) are specific to children.

Benefits of trial participation

Participants in randomised controlled trials (RCTs) derive many benefits, including access to new treatments that might not be routinely available. The Declaration of Helsinki requires that treatment offered to the control group should be the current best standard treatment, and that those allocated to the experimental group receive a treatment proposed to be as good as or

better than standard treatments.⁷ Hence, a well-designed RCT could arguably offer a patient the optimum treatment approach.^{8,9} However, studies that breach this provision are still sometimes done to gain regulatory approval.¹⁰

There might be additional benefits for patients who receive treatment at a hospital or institution involved in RCTs. In studies in adults, doctors who participate in clinical trials are more likely to incorporate trial findings and published data into clinical practice.¹¹ Many reports show inclusion benefits for all trial participants, including children (the Hawthorn effect).^{5,12,13} Participants of RCTs, including those assigned to placebo, have outcomes similar to or better than those of eligible non-participants. Participants have lower mortality, fewer clinical events, and lower complication rates than similar patients treated outside RCTs. This "survival advantage" is not explained by differences in pre-treatment disease status or factors of known prognostic importance.¹⁴ In some instances, the advantage might represent volunteer bias, but it could also be due to closer monitoring and better care of trial participants.

Search strategy and selection criteria

We did a comprehensive search of scientific reports including the databases MEDLINE (January, 1966–June, 2003) and Embase (January, 1980–June, 2003) using the terms children and clinical trials, with translation of relevant articles in non-English language articles. We also undertook hand-searching of reference lists of relevant studies, reviews, and proceedings of scientific meetings, and a search using the Google search engine which identified some important issues about clinical trials in children, which we discuss.

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Risks of trial participation

Along with benefits, there are also potential risks and inconveniences for trial participation. Potential risks specific to children, that are not usually of concern when considering studies in adults, include discomfort, inconvenience, pain, fear, separation from parents or familiar surroundings, effects on growing or developing organs, and size or volume of biological samples.¹⁵ Pragmatic clinical trials, which do not impose a burden of treatment, testing, and monitoring greater than routine clinical care, are designed to obviate additional risks for trial participation.¹⁶

What constitutes an acceptable risk for a child participating in research?^{17,18} Most guidelines for research in children draw a distinction between therapeutic and non-therapeutic research.^{15,19} Although direct benefits to trial participants is not the main intent, therapeutic research is defined as research which could result in direct benefit to the participant, whereas non-therapeutic research produces knowledge of general importance without any direct benefit to the participant. Higher degrees of ethically permissible risk are allowed in therapeutic research (versus non-therapeutic research) involving children.^{15,20,21} Parents are prepared to take greater risks in trials that address the treatment of their child's condition (but not necessarily trials that deal with prevention, screening, side-effects, or quality of life issues) because they highly value having their child's illness cured or improved.²²

Public policy

The importance of clinical trials in children^{23,24} is increasingly recognised by major research groups and professional bodies worldwide such as the National Institutes of Health (NIH)²⁵ and American Academy of Pediatrics (AAP) in the USA,¹⁵ the Medical Research Council (MRC)¹⁹ and Royal College of Paediatrics and Child Health (RCPCH)²¹ in the UK, the European Agency for the Evaluation of Medicinal Products (EMA),²⁶ European Commission,²⁷ and European Federation of Pharmaceutical Industries and Associations (EFPIA)²⁸ in Europe, and National Health and Medical Research Council (NHMRC)²⁹ and Royal Australasian College of Physicians (RACP)³⁰ in Australia. All these groups have recently published policy statements on the importance of assessing health-care interventions for use in children through randomised controlled trials. Such statements are helpful but not sufficient to ensure the ideal becomes reality, unless there are new funding, regulatory, and legislative structures established which can overcome the market-driven bias towards adult-based trials.

The USA has been an example of what is needed worldwide. In 1998, the NIH issued a policy requiring inclusion of children in "all human subject research conducted or supported by the NIH" unless there are scientific or ethical reasons to exclude them,²⁵ to

increase the enrolment of children in research studies. The US Food and Drug Administration's (FDA) Pediatric Rule of 1998 requires evidence from RCTs before new therapies or new indications for existing therapies are approved for use in children. At the same time, the US government attempted to provide financial incentive for pharmaceutical companies for paediatric drug development by introducing the FDA Modernization Act (FDAMA) Pediatric Exclusivity Provision (Nov, 1997–Dec, 2001), which was reauthorised as the Best Pharmaceuticals for Children Act in 2002.³¹ This Act offered an additional 6-month market exclusivity to existing patents for all formulations of any products that have been trialled in children, whether appropriate for paediatric use or not. As a result of these recent changes in regulations and legislation in the US, more trials have been done in children in America in the past 5 years than in the previous 30 years,³² with resulting improved safety information as well as dose changes for paediatric prescribing.³ However, the cost of paediatric exclusivity means that pharmaceutical companies have often focused on drugs that have a large adult market, and patients (usually adults) pay higher prices for brand-name medications for a longer period.³³ There is concern that the distribution of drugs tested is not proportional to the need for these drugs in paediatric care, with over a quarter being cardiovascular drugs.³⁴ The US government has set up a publicly funded programme for the clinical testing of off-patent medications and medications that are still under patent, for which more information regarding paediatric use is needed.³¹

The Pediatric rule was challenged in court and struck down on Oct 17, 2002 (Cruzman SM, Food and Drugs Administration, personal communication) on the grounds that it exceeded the FDA's statutory authority to compel pharmaceutical companies to test their drugs in children. The FDA, in response, called for Congressional support. On Nov 19, 2003, the US House of Representatives approved the Pediatric Research Equity Act (Bill S.650),³⁵ giving the FDA the authority to mandate paediatric studies in specific defined conditions, provided that either the drug is widely used or is considered a therapeutic advance. The codification of the Pediatric Rule now awaits presidential signature. The new legislation, working in synergy with the exclusivity provisions, now may bring us one step closer to the goal of having adequate dosing and safety information for children in the USA. It is too early to tell whether the hoped for effects on children's participation in trials will be realised.

There is currently no legislation regarding paediatric licensing in any other countries. In December, 2000, the European Union Health Council adopted a resolution calling on the European Commission to develop similar incentives and other measures to ensure that new and

existing medicines are adapted for paediatric use in Europe. However, a concrete legislative proposal is still to come from the European Commission.^{28,36}

Drug development priorities tend to be driven primarily by political and economic influences, and the needs of children receive secondary consideration.³⁷ Licensing and funding regulatory bodies in individual countries must take a lead from the USA and demand trial-based data in children for pharmaceutical and non-pharmaceutical interventions of clinical value to paediatric patients before the necessary approvals are given. A systematic co-ordinated process needs to be established worldwide to ensure that the most important or essential drugs are prioritised for paediatric development,³⁷ with ownership and participation by government bodies, industry representatives, and paediatric medical specialty bodies. Only this level of incentive will be sufficient to change the current “optional” attitude prevalent in the pharmaceutical and research community regarding the participation of children in trials.

The ethics of consent for children

There is a tension between the need to safeguard the health of an individual child and the obligation of society to facilitate research that will result in improved outcomes for children in the future.^{38,39} When considering trial participation, parents and paediatricians are usually more concerned about the risks and benefits for the individual child than any societal benefit.^{22,40} The Nuremberg Code, formulated in 1947 in response to the inhumane experimentation in Nazi camps,⁴¹ is the basis for ethical guidelines for research involving human beings. This code requires informed consent for research participation but does not address the issue of children. The Declaration of Helsinki⁷ allows for proxy consent from the legally authorised representative for children’s participation in research, but also stipulates assent from the child if able.

In paediatric trials, consent is obtained by proxy from the child’s parents or guardians.^{15,19,20} Parents are uncomfortable with this referred responsibility because of concerns about unknown or unexpected future side-effects and the possibility that the treatment their child receives might later be discovered to be ineffective or even harmful.²² Some parents acknowledge being more reluctant to consent for their children’s participation in trials than if they were being asked to consent for their own participation.²² Many guidelines stipulate that the child’s assent should also be sought if they are old enough to comprehend the relevant issues.^{7,15,21,42,43} Although parents are happy to share decision-making regarding trial participation in less serious situations, they want to make the final decision for treatment trials of life-threatening conditions,²² highlighting the complexities of proxy consent when parents can override a child’s wishes.

Almost 25% of paediatric trials offer payment for a child’s participation in research.^{44,45} This can be in the form of reimbursement, compensation, appreciation, or incentive payments. However, there appears to be no clear distinction between these forms of payment. Payment for a child’s participation in research is allowed in the USA^{15,46} but is illegal in many countries including those in Europe.⁴⁷ There is concern that payment might distort both the parents’ and children’s decision-making.^{43,48} However, non-reimbursement for additional costs may create unnecessary financial obstacles to trial participation. Most large-scale trials involving adults are funded by the pharmaceutical industry and include a per-recruited patient incentive payment to the investigators to cover costs (“finder’s fees”).

In addition to more prescriptive legislation mandating trials involving children, high ethical standards, and the education and training of investigators in good clinical practice, the protection of human beings in trials are also needed. The ethical obligation to assess interventions in children should override drug profitability projections.

Institutional review boards/independent ethics committees

Central to ensuring the protection of child subjects is the careful ethical review of research protocols at many levels by researchers, funding and scientific bodies, and research ethics committees.²¹ The institutional review board (IRB) or independent ethics committee (IEC) are charged with the responsibility of ensuring that the associated research risks are reasonable in relation to the potential benefits and knowledge to be gained.^{49,50}

A review of the IRB system in the USA shows that IRBs are under-resourced, over-burdened, and ill-prepared to handle the sheer volume and complexity of research that they are asked to review.^{51,52} IRBs commonly tend to focus unduly on procedural aspects and the paperwork requirements of compliance, monopolising resources and contributing little to patient protection. Paediatric expertise and patient and family representation is often absent in the membership of IRBs. Another serious concern is the inconsistent interpretation of regulations and lack of education and training of IRB members in common ethical principles and standards, particularly as they apply to children.⁵¹ There are fewer data on the European situation.

Currently there seems to be no coherent conceptual framework or criteria for judging whether the risks of research are reasonable in relation to what might be gained by the (child) research participant or society. Determining the level of risk is central to the framework on which ethics review is based. Yet, there is no agreement on the definition of what constitutes “minimal risk” and “minor increment over minimal risk” nor on how these definitions apply to different study populations (eg, sick children enrolled on

therapeutic trials versus healthy volunteer children).^{17,21,53} Guidance in this difficult area came from an Institute of Medicine (IOM) report on paediatric research published on March 26, 2004 (<http://www.iom.edu>). The report addresses the need for creation of a robust system for protection of child research participants, providing appropriate paediatric expertise in the design, review, and conduct of studies involving children, and encouraging the inclusion of children in research when it is scientifically and ethically inappropriate.

Clinical trials versus clinical practice

The public perception of clinical trials as experiments, in which people are treated as human guinea pigs has led to a misleading distinction being made between clinical practice and clinical research.^{8,54} It often seems more acceptable (to doctors, parents, and IRBs, because of their self-limited frame of reference) to use untested medications on children as “routine clinical care” rather than enrol eligible children in a relevant clinical trial, in which the effects of interventions can be monitored and analysed to provide valid information on the benefits and harms of the intervention.^{22,40} Isolated instances of death in children participating in research trials, although tragic on a personal level, serve as sentinel events that trigger public reaction against human “experimentation”.⁵⁵ These events are evidently more newsworthy than the same outcomes in the setting of “routine clinical care” and success stories from trials tend to be under-reported.

A double standard exists, whereby treatments given outside clinical trials are less stringently reviewed than protocol treatments given within the trial context. In reality, many medications given to children are off-label (ie, prescribed for children despite being approved only for adults), unlicensed for use in children, and without adequate pharmacokinetic or safety data regarding use in children.^{5,56–59} For example, several years ago, only five of the 80 drugs most frequently prescribed for children in the USA had FDA-approved paediatric indications.⁵⁹ The American Academy of Pediatrics has stated that treating children with untested drugs might place more children at risk of harm than including them in controlled studies of the drugs.⁶⁰ Not to undertake clinical trials in children might “deny children the benefit of optimum treatment, or worse still, cause harm from unpredicted adverse events”.⁶¹

The optimum timing of paediatric studies depends on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatment. Investigations should be done during the early phases of development for therapies for treating serious or life-threatening diseases for which there are few therapeutic options or for diseases predominantly affecting children, and during later phases for therapies for other diseases and conditions.²⁶ Some paediatricians believe that offering

trials to adults before offering them to children delays and deprives children of potentially useful therapy.^{23,40} Others have argued that when clinical equipoise exists (ie, when there is collective uncertainty within the expert medical community about the relative merits of alternative treatments), it is unethical not to recommend trial entry to eligible patients, because it implies the doctor knows the best treatment despite the lack of scientific proof.⁸

Why are so few children involved in trials?

Given the smaller pool of patients available for trials in children, the higher fixed and marginal costs are a major disincentive for the pharmaceutical industry to fund trials in children, particularly when the market size at the end of an expensive research and development programme is often small. The most common excuses for failure to do paediatric studies are the high cost of the studies compared with the size of the potential market, the difficulty of finding enough patients to participate, the complex ethical issues associated with studying children, and inadequate numbers of quality paediatric pharmacology investigators.⁶²

Small trials are usually inadequately powered to detect small or moderate treatment effects that might be of clinical significance.⁶³ Although not unique to paediatrics, the problem of underpowered studies is more pronounced in children because of their smaller burden of disease. This is shown by a study reporting trials published in a major UK-based general paediatric journal from 1982 to 1996, in which half of the trials recruited fewer than 40 children.⁶⁴

Strategies to increase children’s participation in clinical trials include increasing paediatric participation in large multi-centred trials of all ages as well as increasing the number of children-exclusive trials. “Piggy-backing” a trial in children onto a predominantly adult trial as a specific sub-study can allow investigators to formally test whether age is an effect modifier but risks insufficient attention to the paediatric group of the study, so that child-specific factors such as critical dose-response relationships in safety and efficacy and other practicalities relevant for children are neglected. Inadequate representation of children in predominantly adult trials means that the results are often not generalisable for children.⁶⁵

Recruitment issues are postulated to be quite different for paediatric and adult trials.⁶⁶ The recruitment of children is thought to be more difficult than that of adults,⁶⁷ with the exception of paediatric oncology trials.^{66,68} The reasons for low accrual rates in many paediatric trials are multi-factorial, and relate to doctor, parent, child, and trial factors.^{22,40}

Doctor factors

Parents and paediatricians acknowledge the important influence that paediatricians have on a parent’s decision

regarding trial participation.^{22,40,69} When recruiting adults to clinical trials, the reluctance of the primary treating doctor to enrol patients is a major reason for poor recruitment rates.^{70–72} This is thought to stem from their perceived conflict between their roles as caregiver and scientist.^{54,73} Other common barriers include forgetfulness or lack of awareness of trials that are open for accrual,^{74,75} time^{74,76,77} and financial constraints,⁷⁸ extra work involved for physicians,⁷⁹ lack of resources,⁸⁰ lack of rewards and recognition,^{73,81} difficulty with ethics requirements and informed consent,^{76,79,80,82,83} concerns about the effect on the doctor-patient relationship,^{76,82–84} fear of losing patients,^{75,76,85} concerns about the patient's wellbeing,⁸⁵ discomfort with randomisation,^{85,86} preference for a particular treatment,^{76,77,83,85} dislike of loss of autonomy,⁸² dislike of open discussion involving uncertainty,⁷⁶ and mistrust of researchers.⁷⁵ Although there has been less work on barriers to recruiting children to clinical trials, paediatricians also acknowledge similar concerns.^{40,87}

Parent factors

In paediatric trials, parental consent is required for children's participation. The balance of perceived benefits and barriers or risks of participation, and the importance of the study influences parents' willingness to participate.^{22,88,89} Perceived benefits for parents include the opportunity to access new treatments, better care being given to their child, gaining greater access to health-care professionals and health information, meeting others in similar circumstances, gaining hope when no other effective treatments are available, and the satisfaction of knowing they are helping other children in the future. Parental barriers to participation include protective parental instincts, fear of their child being treated as a "guinea pig", anxiety about the unknown factors inherent in research, and concern that researchers' priorities might not be in the child's best interest. Perceived risks include known and unknown side-effects, the chance that their child might be randomised to an ineffective treatment, and the inconvenience of participation (eg, extra blood tests, time demands, clinic visits).^{69,89–92}

In one study, researchers noted that parents who volunteer their children for clinical trials are less educated and from lower socio-economic groups, have less social support, consume more habit-forming substances, and display greater health-seeking behaviour than do parents who decline to have their children take part.⁹³ By contrast, other investigators recorded no such associations between parental sociodemographic characteristics and recruitment.⁸⁹ Sociodemographic factors can affect a doctor's willingness to approach or refer particular patients (eg, those who are middle class and educated) because of easier communication and a perceived likelihood of participation.⁴⁰

Child factors

The child's health status modifies the risk-benefit balance for parents. Although many paediatricians think parents will be less willing to participate in trials if their child's illness is severe,^{40,87} the reverse has been found to be true.¹⁴ Parental consent for trials is higher during a child's acute illness. For example, recruitment rates were higher for admitted inpatients or children recruited from the emergency room compared with those identified through outpatient records.⁶⁹ Similarly the proportion of parents who enrolled their baby into a clinical trial which needed early entry was higher than those who enrolled in a study which asked for later consent (71% vs 43%).⁹⁴ These differences in consent rates may reflect parental response to a "sense of urgency" during their child's acute illness. Children generally view trial participation as a positive experience, citing altruistic reasons, age-appropriate incentives, and seeking a fun experience as motivations for participation. However, children dislike needles, blood tests, bad-tasting medicines, and interruption to their normal routine.^{95,96}

Trial factors

There is poor awareness and understanding of paediatric RCTs by parents.^{40,69,97–99} The rationale for the random allocation of treatment and the use of placebo is generally poorly understood by adult doctors,⁷² paediatricians,⁴⁰ adult patients,¹⁰⁰ and parents.^{22,98} Because of this confusion, the presence of a placebo group is often a barrier to trial participation,¹⁰¹ and is viewed by some to be unethical for life-threatening illnesses.^{22,40} Although they are less common, many parents and doctors prefer non-inferiority or superiority trials with active treatment arms.^{22,102}

Parents often have a poor understanding of the informed consent process.^{22,69,98,99,103} Many have difficulty understanding the consent form and find the wording frightening.²² The readability factor might also compromise the informed consent procedure.¹⁰⁴ Improving the clarity of the consent form, and investigators giving extra attention and information to parents could aid parents' understanding (especially if there are linguistic or cultural differences).¹⁰³ Protocols for RCTs have been criticised for being too restrictive.⁷⁶ The recent development of pragmatic trials, in which investigators measure the effectiveness of the treatment in routine clinical practice (rather than the efficacy of treatment under ideal conditions)¹⁶ might be more acceptable to paediatricians.

Many aspects of trial design need to be addressed to ensure adequate recruitment of paediatric patients. The trial design needs to be acceptable to both paediatricians who will refer children, as well as parents and children who will participate. The use of pragmatic trials and non-inferiority trials whenever possible, improving the consent process and minimising disadvantages of trial

participation (such as unnecessary blood tests and hospital visits), and making participation more convenient for paediatricians and families (by offering home visits, travel cost reimbursements, and by reducing the paediatrician's workload with a designated trials coordinator) will encourage participation.^{22,40}

Participation in paediatric oncology trials

The participation of children with cancer in clinical trials has become increasingly common since the 1970s, and is arguably responsible for the large increases in cancer survival observed since then. Highly significant increases in 5-year survival rates for common childhood cancers were noted in a population-based series of more than 15 000 childhood cancer cases registered in Great Britain from 1971 to 1985 (eg, from 37% to 70% for acute lymphoblastic leukaemia, from 22% to 70% for non-Hodgkin's lymphoma, from 15% to 43% for neuroblastoma, and from 17% to 54% for osteosarcoma).¹⁰⁵ These improvements in survival took place when increasing numbers of children with cancer were being treated at specialist centres that were participating in national and international clinical trials. The same decline in death rates for most childhood cancers has also been seen in the USA.¹⁰⁶

Childhood cancer is rare, and referral patterns to tertiary (usually academic) centres are well-established. Paediatric cancer centres have long been organised into national and multi-national paediatric cancer cooperative groups, in which high proportions of incident paediatric cancer cases in the population are enrolled into clinical trials. Ross and colleagues¹⁰⁷ analysed 21 026 incident paediatric cancer cases diagnosed in the USA from 1989 to 1991, and noted that about 94% of children younger than 15 years who have been diagnosed with cancer are seen at an institution that is a member of either the Pediatric Oncology Group or the Children's Cancer Group,¹⁰⁷ which merged in 2001 to form the Children's Oncology Group, a clinical trials organisation of more than 235 hospitals in North America and worldwide. Through such paediatric cancer trial groups, the power of systematic clinical trials to improve outcomes has been well identified.¹⁰⁸

In view of the evidence from the paediatric oncology experience that participation in protocol-driven clinical research is clearly better than the ad hoc patterns of non-protocol treatments, paediatric cancer trials offer a paradigm for paediatric clinical research. The benefits for the participants of paediatric cancer clinical research are numerous¹⁰⁹ and include the rigorous process of protocol development, incorporating review at many levels and incorporating best practices, commonly centralising pathology review and radiation therapy planning, and mandating close adherence through audits and review of performance. Response and toxicity are closely monitored and pooled through a unified database, and investigators develop long-term research

relationships, often undertaking a series of clinical trials. This creates a powerful empirical force for adjusting treatment regimens and improving outcomes in each subsequent trial, which, together with widespread participation in trials, has created a culture in which there is almost a fusion between clinical research and clinical practice in paediatric oncology. The high participation rate in clinical trials of children with cancer (more than 50% of the US children who receive their care at institutions that are members of paediatric oncology groups)⁶⁶ stands in striking contrast to the mere 2–3% of adults with cancer who are participating in trials.¹¹⁰ There are a range of practical as well as philosophical reasons for the low rates of accrual to adult oncology trials, such as more widely dispersed and variable patterns of cancer care providers, as well as economic pressures.¹¹¹

The future for paediatric trials

Better education of the medical community and the public is needed about the rationale and benefits of trials and the potential dangers of using health-care interventions that have not been appropriately studied. Negatively biased media coverage about clinical trials involving children needs to be balanced with public-awareness campaigns with positive stories about the societal benefits of RCTs, highlighting the possible harm from unpredicted adverse events because of a lack of paediatric trials.

Because of the difficulty encountered in recruiting children to clinical trials, researchers need to take into account the risk-benefit analysis parents make when considering their child's participation in trials and, accordingly, modify risk factors and costs whenever possible to enhance participation—eg, by keeping blood tests and hospital visits to a minimum, and by reimbursing travel and other costs. Researchers must also build better relationships with paediatricians and parents by communicating more clearly and openly. They need to address key issues such as the parents' emotional response to their child's involvement in a trial, and the physician's concerns about trial participation disrupting their doctor-patient relationship. As the need and demand for paediatric clinical trials increases, researchers must find strategies to overcome both the parents' and doctors' barriers to trial participation.

Structural external changes that would help improve clinical trials in children include the development of co-operation between institutions, similar to the co-operative paediatric oncology groups, the Pediatric Pharmacology Research Unit (PPRU) Network⁶² and the MRC's General Practice Research Framework for adults in the UK.¹¹²

Suggestions for improving the function of IRBs and IECs include providing adequate resources and funding by government and research agencies,⁵² and to centralise

IRB review and monitoring activities, especially those dealing with large multi-centre research protocols, thus pooling resources and appropriate expertise. Such centralisation has the potential to generally improve efficiency, reduce duplication of effort and costs, and save time. The monitoring of adverse events across trial sites and central review would also enhance patients' safety in multicentre trials, because local IRBs are unable to assess the relevance of a single adverse event in the context of the entire trial population. For IRB functions to be centralised, policy reforms and relief from fear of institutional liability must be forthcoming from federal agencies. The preliminary experience with a central IRB for US National Cancer Institute-sponsored clinical trials for adults with cancer, which involves more than 150 sites, is encouraging.¹¹³ Experience from this pilot central IRB project should be considered when multi-institutional paediatric ethics review committees are set up.

The development of a national or international infrastructure for clinical research, and the provision of infrastructure support to assist with the recruitment and co-ordination of trials in individual centres, supported and funded by government and national research agencies will also improve the conduct of paediatric trials.

Translating clinical research into clinical practice continues to be a challenge. Although there are policies to promote the inclusion of children in clinical trials, their involvement continues to be difficult because of the lack of infrastructure and support for research, the regulatory and compliance hurdles for the protection of human participants, and the dire shortage of investigators with an interest and expertise in paediatrics and clinical research. Trials involving children are on trial. This is particularly alarming at this juncture in health research, when the fruits of our investment in basic biomedical research should be being realised. Children might be left behind if government, researchers, and industry conclude that it's just too hard, too complicated, too risky, and too expensive. Children deserve better.

Conflict of interest statement
None declared.

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