Paediatrics

Anne Cusick
*University of Wollongong, acusick@uow.edu.au*

Natasha Lannin
*Cerebral Palsy Inst, Uni of Notre Dame Aust, Sydney*

Iona Novak
*Cerebral Palsy Institute, Sydney*

Publication Details
Paediatrics

Keywords
paediatrics

Disciplines
Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

This book chapter is available at Research Online: http://ro.uow.edu.au/hbspapers/836
Paediatrics

Anne Cusick,1 Natasha Lannin,2 and Iona Novak3

1School of Biomedical and Health Sciences, University of Western Sydney, Sydney, Australia
2Rehabilitation Research Studies Unit, Faculty of Medicine, University of Sydney, Sydney, Australia
3Cerebral Palsy Institute, Sydney, Australia

Contents

10.11.1 Introduction 628
10.11.2 Definitions 628
10.11.2.1 Paediatric Population 628
10.11.2.2 Off-Label Use 628
10.11.2.3 Therapeutic Orphan 629
10.11.2.4 Paediatric Investigation Plan 629
10.11.2.5 Minimal Risk 629
10.11.3 Overview of Unique Aspects of Paediatric Trials 629
10.11.4 Conventions 632
10.11.5 Benchmark Regulations 634
10.11.6 Recommendations and Guidelines 636
10.11.7 Institutional Review Boards 638
10.11.8 Trial Questions 639
10.11.9 Participant Characteristics 643
10.11.10 Paediatric Investigation Plans 645
10.11.11 Assent and Consent 649
10.11.12 Safety and Monitoring 652
10.11.13 Conclusion 653
Appendix: Facts Summary 654
References 654

Clinical Trials Handbook, Edited by Shayne Cox Gad
Copyright © 2009 John Wiley & Sons, Inc.
10.11.1 INTRODUCTION

This chapter introduces then explores in detail, issues and practical aspects of the context and conduct of paediatric clinical trials. Investigators need to be alert to the unique obligations that come into play when study participants are infants, children or young people. These obligations are ethical, procedural, legal and social. Investigators also need to be aware of the multiplicity of interests that operate in paediatric research so that projects can be successfully managed to completion. Ideally, realistic and reasonable paediatric trials will cause minimal harm and will meet expectations of parents, caregivers, investigators, sponsors and the public for meaningful and clinically useful outcomes.

This chapter presents the scope of challenges and opportunities in the paediatric specialty, to help support clinical trials that are child-centred, worthwhile and rigorous. Paediatric research is an area characterised by local procedural variation and rapid change in regulation, case-law, scientific evidence, scholarly opinion, public concern and professional guidelines. Consequently, this chapter provides common signposts, rather than prescriptive maps, that can be set in place by investigators as they lead the way in particular trial journeys. By the end of this chapter, investigators should have a breadth of view on issues involved in paediatric trials to enable them to apply technical information to the context of paediatrics. Investigators should also be able to reflect on their own standpoint and responsibility as trial leaders, sponsors or team members who are knowingly putting infants, children or young people at some level of risk in order to answer a question. Investigators should be able to seek out specialized paediatric trial sources after reading this chapter, having first gained a broad understanding of issues that must be proactively managed for successful trial completion.

10.11.2 DEFINITIONS

10.11.2.1 Paediatric Population

The United Nations Convention on the rights of the child [1] defines a minor as anyone under the age of 18. While there are local variations to the legal age of adulthood, and while the clinical responsibility of the paediatric specialty may extend to 21 [2], the UN Convention should normally be observed for the purposes of trial research. For this chapter, the preivable or viable foetus is not included, however these are recognised as responsibilities of paediatrics [2] and specialized research sources should be consulted commencing with policy and guideline statements of relevant bodies for example, the American Academy of Pediatrics [3].

10.11.2.2 Off-Label Use

Many drugs used in paediatrics are off-label and one reason underpinning the need for clinical trials is to reduce this practice:

"new drugs and biologicals [need to] include adequate pediatric labeling for the claimed indications at the time of, or soon after, approval. However, because such labelling may
11.2.3 Therapeutic Orphan

Drugs which are not approved by the Food and Drug Administration [USA] as safe and effective in children are prescribed daily. This is due in part to the fact that many drugs released since 1962 carry an “orphaning clause” in the package insert such as, “not to be used in children, since clinical studies have been insufficient to establish recommendations for its use ...” Is the physician breaking the [USA] law when he prescribes drugs ... which carry the ‘orphaning clause’? No, he is not. The physician may exercise his professional judgement in the use of any drug. However, if he deviates from the instructions in the package insert and adverse reactions occur, he must be prepared to defend himself in court if there is a malpractice suit” [5, p. 811].

11.2.4 Paediatric Investigation Plan

[It is] a development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorisation of the medicine for children. ... The paediatric investigation plan includes a description of the studies and of the measures to adapt the way the medicine is presented (formulation) to make its use more acceptable in children ... The plan should cover the needs of all age groups of children, from birth to adolescence. The plan also defines the timing of studies in children compared to adults. In some cases, studies will be deferred until after the studies in adults have been conducted, to ensure that research with children is done only when it is safe and ethical to do so [6].

11.2.5 Minimal Risk

Minimal (the least possible) risk describes procedures such as questioning, observing and measuring children, provided that procedures are carried out in a sensitive way, respecting the child’s autonomy and that consent has been given ... It is expected that research of minimal risk would not result in more than a very slight and temporary negative impact on the health of the person concerned [7, p. 15].

11.3 OVERVIEW OF UNIQUE ASPECTS OF PEDIATRIC TRIALS

This section overviews key issues that make paediatric clinical trials unique. Paediatric clinical trials seek answers about intervention effectiveness and safety—there is nothing unique about this—but to get answers, these trials are unique in requiring infants, children and youth as participants. The sample characteristics and needs thus dominate trial decisions. Paediatric populations present design challenges for trial
investigators. As participants they have inherent and continuous change in their structures, function, activities and participation, there is constant change in their social relations, exposure to physical environments, family and community influences—this continuous change is evident even when they are in good health. The scale and variability of change increases if there is illness, disease, disability or injury. Continuous underlying change in participants must therefore be anticipated in trial question, design and protocol decisions.

Paediatric populations also bring investigator responsibilities and accountabilities that extend well beyond those normally encountered in trials with adults. Young participants are inherently vulnerable and those who have illness or disability appear particularly exposed to the possibility of suffering. Adults make decisions on behalf of youngsters and act towards them in ways that may harm or harm both their daily life and their life chances. Their vulnerability presents dilemmas for all involved in clinical trials. For adults to purposefully involve youngsters in studies with potential or known risk seems incompatible with obligations to protect and nurture them. For institutions, like hospitals, established to care and help, knowingly exposing youngsters to risk seems a betrayal of civic duty. These moral contradictions are a necessary and inevitable part of paediatric trials. They underpin the heightened emotion and public interest that accompanies paediatric trials. But without sound paediatric clinical trials greater harms may be perpetrated as parents, carers, medical and health personnel use clinical interventions on children at large without adequate or sometimes any scientific evidence to inform their decisions.

Clinical trials must be conducted, but their planning and accountabilities must also anticipate and accommodate paediatric participant vulnerability. Investigators who are aware of this moral context will ensure that questions are not only worthwhile, but also that protocols are explicitly child-centred, of rigorous design, and well conducted. It is the heightened moral context of paediatric clinical trials that is unique as infants, children and young people, not investigators, parents or sponsors, must live with the trial experience and the short and long term consequences of participation. Trial investigators who are aware of the moral context will also anticipate potential public interest and consider in advance how the person might construe issues such as recruitment, design, funding, sponsorship, personnel and study procedures. Paediatric trial project planning thus needs to include strategies for public communication, public liaison and accountability.

The inherent vulnerability also means that a paediatric trial is one where child participants are the focus of many interested parties. Stakeholders include parents and guardians, medical, legal, health, and policy personnel who act as gatekeepers to and watchdogs of paediatric population participation. The media, pharmaceutical companies, organised advocacy and lobby groups play vigilant and vigorous roles in the initiation, public presentation and interpretation of trials. Stakeholder authority and influence can make the planning and conduct of paediatric trials a complex and delicate campaign of personal, professional, industry and community politics—additionally to the usual demands of a complicated scientific project. Proactive communication with stakeholders is needed regarding the question, study rationale, study conduct, regulation adherence, avoidance of conflict of interest, transparency and accountability of processes and records, and importantly the need for trials to
ines and accountabilities in trials with minor illness of disease. Adults make the ways that may help vulnerability present fully involve younger with obligations established to care and of civic duty. These pediatric trials. The companies pediatrics may be perpetuating interventions on evidence to inform their and accountabilities in vulnerability. Involved questions are centred, of the context of pediatric e, not investigating short and long the moral context of pediatrics. Enabling thus: needs and accountability is one where children act as gatekeepers and vigorous stakeholders authenticating in pediatric trials a complex community politics, etc. Proactive consultation, study rationale, rest, transparency, need for trials to prevent current and future suffering caused by the use of interventions that have scientific support.

Pediatric trials necessitate a careful balance of common sense, technical precision, and adherence to highly prescriptive regulation. Given the sensitivity of research with children, successfully engaging in pediatric trials is as much about identifying a moral purpose, communicating trial values and visions, ensuring justice for participants, and scanning the strategic context for threats and opportunities as about the study question, procedural diligence, protocol development and project management.

These "soft" project factors can publicly or professionally derail an otherwise well-timed and well-constructed trial if not proactively managed. They can destroy an investigator's reputation even when no malicious intent or negligence was involved. The "front page of the paper" by-line may be all a public needs to credit a researcher, damage institutional confidence and undermine a much-needed program of pediatric health research. Careful consideration of not only the scientific merit of the question, design and regulatory obligations, but also of the moral politics of pediatric trials is thus required. For some investigators, the interests and authority of stakeholders and gatekeepers seem like obstacles to research, however any experienced trial researcher knows these factors are just part of the "package" that is a pediatric trial.

Pediatric practice is also inherently multidisciplinary and the design of clinical trials must be robust enough to anticipate an array of potentially confounding factors in a child's life emanating from health services, schools, community and family, including parental use of off-the-shelf medications, complementary medicines and alternative therapies. A clinical trial that is child-focused rather than variable focused will take into account the multiplicity of influences that may affect body structures, ability to participate in protocol requirements, recruitment, retention, confounding factors, and the short and long term consequences of trial participation.

Finally, participation, protocol adherence, study retention and the safety of young participants ultimately relies on parent and caregiver expertise and their understanding and commitment to trials. Engaging parents and caregivers as protocol partners is critical to study success. Providing appropriate learning opportunities for parents to understand not only the study purpose and participants demands but also children's rights to assent or decline participation are needed. This understanding goes to the heart of informed consent. Consideration of parent and caregiver perspectives in protocol design is essential, particularly in relation to the logistic and time demands on parents for intervention adherence and presentation of the child for outcome data measure collection. Pediatric clinical trials work better if the protocol can be reasonably integrated into the daily life of families as part of a sustainable routine.

This section of the chapter has provided pediatric investigators with an orientation to unique issues in pediatric trials. The following sections explore issues in more depth, however the following caveats apply. This chapter is introductory. Specialized pediatric sources, such as the Helms and Stonier (Eds) Pediatric Clinical Research Manual [8] which is regularly updated and has sub-speciality supplements, or the many specialty research related web-sites of regulatory bodies or professional societies should also be consulted. Research, scholarship policy and
commentary associated with paediatric research changes quickly. Investigators must therefore ensure they inform themselves about local requirements, contemporary conventions, up-to-date regulation, current public concerns, scholarly opinion, and relevant scientific evidence available at the time of study commencement. A matter of months can dramatically change the paediatric research context as case law, public interest, media “frenzies”, local administration or new evidence can change what could be reasonably expected in an investigation plan. Particular attention should also be given to the most recent scientific evidence emerging from the paediatric sub-speciality under study, be that oncology, cerebral palsy, infectious diseases or whatever, including evidence relating to effective sub-speciality trial methodologies. Different sub-specialities bring unique challenges relating to measurements recruitment, consent and retention. Successful sub-speciality precedent studies can also help inform trial plan decisions. But caution! Precedent studies may have been conducted in different regulatory and social contexts making their methodologies unsuitable for contemporary replication even though the scientific findings may be rigorous and relevant.

The remainder of the chapter begins with the policy context. Policies have been developed to protect vulnerable infants, children and young people in research and to promote ethical practice. Conventions, regulations, recommendations, guidelines, and institutional review boards are introduced. The chapter continues with an exploration of issues that are particularly challenging in paediatrics: the questions, participant characteristics, investigation plans, consent, assent, safety and monitoring.

10.11.4 CONVENTIONS

Regulatory requirements compel investigators, sponsors and research partners to scope and conduct research in certain ways. Investigators and trial partners must comply with regulations or face consequences that may include prosecution and penalties ranging from public “naming and shaming” to fines or in cases of criminal conduct imprisonment. The existence of regulations means that clinical research not only be weak or rigorous, it can also be lawful or unlawful. Investigators and members of institutional ethical review boards therefore have a duty to keep up-to-date with regulatory requirements as ignorance is normally no excuse. Understanding legal obligations, particularly those for paediatric populations, is as important as understanding scientific methods and the needs of youngsters. Investigators cannot work on the basis of what has been done in past practice or research, nor can they apply the same level of autonomous discretion they may use in their clinical life, as research-related regulations change over time, the standards for research decision-making are more prescribed and tests of due diligence, fair hearing and procedural fairness in research may be tighter.

A good place to start in understanding the regulatory context of paediatric research is with landmark conventions. These state agreed international positions on matters of importance that relate to the human condition. The United Nations (UN) General Assembly “Convention on the Rights of the Child” 1989 is probably one of the most important foundations for the paediatric speciality [1]. Although...
not all countries have ratified this convention, the influence of the convention on national standards is enormous. In summary, the convention identifies that: human rights apply to children without exception; the child’s best interests are the primary consideration and highest priority; children have a right to the highest attainable level of health; and they have a right to information and respect of their opinion [1]. While clinical trial plans would almost never cite the Conventions on the Rights of the Child as a methodological source and there is no mechanism to directly register trials as convention compliant with the UN, it is principles in this convention that local regulations around the world usually aim to embed and enforce.

Practically, investigators can use this convention to reflect on whether or not their study question or plan is “just”. Investigators have a duty to act justly towards participants [9] and tests of justice may go beyond local regulatory requirements. The convention can provide some insight into what might reasonably be considered just. If one accepts the principle that children everywhere in any society should have human rights, then just study protocols should seek to preserve and protect those rights. Just protocols will thus include strategies to inform, listen to the opinion of and seek assent of child participants, even when parental permission has already been granted. The principle of “best interests of children”, if accepted, also means that the best interests of child participants and children in general are high priorities in study decisions. In some ways children must benefit, whether that is directly through trial participation or indirectly through study outcomes that enhance the well-being of children in general. Finally, the just trial will support the principle that children have a right to the highest attainable health, particularly in relation to weighing up trial benefits and risks to individual children and children in general.

Other international agreements relating to research may also apply to paediatric investigation. The most notable is the Declaration of Helsinki [10]. Clause 25 specifically relates to child involvement in medical research and it focuses on consent and assent. The United Nations Convention on the Rights of Persons with Disabilities [11], and the Declaration on the Rights of Indigenous Peoples [12] may also be relevant for studies that have targeted or incidental recruitment of youngsters from these groups. Both these conventions are relatively new, and not all countries are signatories, but again they provide a benchmark for investigators to consider whether not the study question and plan is “just”.

Conventions are thus an important and useful background to investigator development of an ethical standpoint towards young participants. They help identify what might be considered just treatment. But most investigators do not use them. Instead they follow local regulations and procedures that codify ethical requirements. Local regulations may or may not be adequate for the moral context of paediatric clinical trials. Here is where the utility of “benchmark” regulations comes into play for investigators around the world. Although they may not apply locally, benchmark regulations provide guidelines and procedures that usually embed principles from conventions or declarations in their construction. Benchmark regulations can thus act as a guide, along with local requirements, for investigators to consider what a reasonable person would expect in a just paediatric study. The benchmark regulations of most influence are now explored. Both relate to medicines for children however the principles and processes are useful to inform research-
ers who work with other clinical interventions as they highlight the need for clear standards, accountabilities and procedural precision.

10.11.5 BENCHMARK REGULATIONS

One of the most significant developments in Twenty-first century paediatric clinical research has been the release of regulations in the European Union (EU) and the United States of America (U.S.). While other countries have local standards and regulations that must be consulted by investigators and adhered to in plan development and reporting, the sheer scale of the EU and U.S. regulations impact numbers of trials and participants makes them global benchmarks that can inform and guide clinical trial decisions anywhere. This section first overviews where regulations and related sources are located, as any paediatric investigator will need to continually update and check rulings and applications of regulations. Then the EU and USA regulations themselves will be introduced, and examples of regulations from other jurisdictions that may be helpful will be provided.

The regulations and support material of the EU are easily located. A web-search using any popular search engine and the general term “paediatric clinical trial” will reveal links to the European Agency for the Evaluation of Medicinal Products (also known as European Medicines Agency, EMEA) (http://www.emea.eu) in addition to independent sites that hold related articles, opinion pieces, conferences and training announcements on the general topic of paediatric clinical trials and often the EMEA initiative specifically. These related items can be EMEA sponsored, or independent and they often maintain a lively watch on the EMEA initiative from an investigator and industry perspective. Sites such as these, together with subspecialty resources in particular fields available through scholarly journals, professional societies and consumer groups, help investigators understand the motivations, agendas, obligations and impacts of the EU regulation from a broader perspective. The latter can help inform the strategic decisions that need to be made by trial leaders in project planning and management. From the home page of the EMEA Medicines for Children a wealth of official resources is also available to investigators including the regulation itself, guidance for applicants, access to scientific advice, decisions and opinions on applications and importantly, paediatric related information. The latter includes information on paediatric needs, clinical trials, priority list of off-patent medicines and presentations. Importantly, the decisions and opinions on particular trial applications, including class waivers and product-specific decisions are included on this site.

The EU Regulation (EC) No 1901/2006 amended, the “Paediatric Regulation”, came into force in January 2007, and investigators, industry and the public are still exploring the material effect it may have on paediatric research activity. The paediatric regulation aims to increase the number and availability of medicines that can be used in the paediatric population, by providing rulings, guidance and incentives to investigators, sponsors and institutions to develop paediatric specific products and to develop paediatric prescribing information for other medicines. Mechanisms to license and provide clinician and parent information are also included. One of the features of the Paediatric Regulation is the establishment of a new Paediatric Committee of the European Medicines Agency [13]. This scientific committee has
the need for deci-
ded. A web-search
clinical trial's
ual Products (physi-
als and on the
sented, or inde-
A initiative togeth-
journals, prof-
minister perspec-
y begin to investi-
ated and opin-
specific deci-
tric Regulation's
public are
edicines that
and incentive
pecific product
Mechanisms
clusion. One
a new Paediat-
c committee
the authority to make decisions and provide opinions on applications to do research and on outcomes of that research in relation to product use. The Committee is multi-disciplinary, brings together renowned experts in fields of general practice, paediatric medicine, pharmacy, pharmacology, research, pharmacovigilance, ethics and public health. Health care professionals and patient associations are also part of the collective expertise.

The Paediatric Committee has an onerous task to ensure paediatric medicine game approval is based on rigorous quality, safety and efficacy data. Strategies used by the Committee include: requiring paediatric investigation plans (PIPs) and data to be submitted to regulatory authorities; assessing PIPs and providing decisions and opinions; monitoring of the PIP compliance; supporting a paediatric research network; implementing key public communication strategies such as the use of a common symbol for medicines that have an approved paediatric use; and training investigators. In addition the regulations provide an incentive to investigators and sponsors by providing an additional six months on the supplementary protection certificate if completed PIP information is included in the Summary of Product Characteristics. For off-patent products, there is the incentive of a paediatric use marketing authorisation which has a ten year data and market protection period. The regulation also provides for establishment of a European data base of paediatric clinical trials, part of which will be publicly available.

Access to U.S. regulations is less straightforward. There are multiple web-routes to access relevant information, and the best route will depend upon the study ques-
One is to go direct to the U.S. Department of Health & Human Services (HHS) (http://www.hhs.gov), thence to the Office for Human Research Protections (OHRP) (http://www.hhs.gov/ohip/). Another is to start with the U.S. Food and Drug Administration (FDA) (http://www.fda.gov) and consult the various pages to do with clinical trial practice that may include adults as well as children (http://www.fda. cd/cber/pediatric). One page, for example, provides direct links to all FDA regulations relating to good clinical practice and clinical trials (http://www.fda.gov/cber/gcp/regulations.html). There is also the Office of Pediatric Therapeutics (http://www.fda.gov/cber/pediatric).

The history and recent state of USA regulations that inform paediatric research has been reviewed by Diekema [14]. He provides a concise guide to critical incidents and key sources, most notably the Code of Federal Regulations, 45 CFR 46, Subpart D, Additional Protections for Children Involved as subjects in research 1983. Others are the Best Pharmaceuticals for Children Act 2002 and 2007 [15], and the Pediatric Research Equity Act 2003 [16] that re-established the FDA's authority to mandate pediatric drug development [17]. Informative guides and regular updates on paediatric issues have been developed and are available through HHS sites of the OHRP and FDA. An example is the Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA under 21 CFR 314: Additional Safeguards for Children in Clinical Investigations [18]. Apart from linked guidelines, these sites provide "current thinking" of the agencies in relation to key issues variously presented as "frequently asked questions" or "guidelines".

Other they provide aide-memoirs for investigators such as the "pediatric points to consider" that include a summary of unique review concerns for paediatrics, including study justification, study design, ethical issues, and pediatric protocol checklists. Later stage trial results should be reported to the clinical trial registry
and database in accord with Regulation S3807. There are also incentives in regulations to encourage paediatric pharmaceutical research, such as six month exclusivity on manufacturer marketing licensing if the company “fairly responds” to FDA requests.

While the OHRP site provides guidance and recommendations for paediatric study conduct, it also highlights areas where compliance is required under the US HHS Regulation. Compliance is specifically required for HHS supported research, but the aspects identified may provide useful benchmarks to alert investigators outside the HHS or USA for potentially high stake paediatric trial issues. As thinking may change and as there is acknowledgement that alternative approaches may be considered by the authorities, investigators are advised to check these sites for changes, opinions and rulings as part of trial planning.

Internationally, many countries have regulations that apply to research with human subjects and specifically to paediatric populations. Most feature principles and practice requirements or recommendations that are consistent with the broad approach of the EU or U.S. and related international conventions. Australia, for example, has the National Health and Medical Research Council statements including the Australian Code for the Responsible Conduct of Research [19] and the National Statement on Ethical Conduct in Human Research [20]. Canada has the Medical Research Council Tri-Council policy statement on Ethical Conduct for Research Involving Humans [21]. Some other countries have statements on the conduct of research in humans, but have little that specifically relates to paediatric populations. For example, India has the Ethical Guidelines for Biomedical Research on Human Participants [22]; and South Africa has a Code of Research Ethics [23]. Both have only limited clauses relating to child research.

In addition to benchmark and local regulations for paediatric research in general, investigators need to be alert to any special provisions for particular groups. In Australia, for example, there are particular guidelines and requirements for research involving indigenous people [24]. Other countries may have similar provisions that should be consulted and integrated into PIPs. There are also special provisions in Australia for research that is conducted outside the country [25] and similar approaches may be taken in other nations. The particular vulnerabilities of unaccompanied children, foster children, wards of the state, and emancipated children also need attention if they are to be target or incidental participants. A lack of attention to any of these regulations can have a significant impact on the conduct of a trial or the reputation of investigators, sponsors or institutions involved.

10.11.6 RECOMMENDATIONS AND GUIDELINES

In addition to regulatory requirements and recommendations from statutory government sponsored institutions, trial investigators, coordinators and employees may also need to be registered or accredited professionals, subject to the Code of Conduct, recommendations, guidelines or prescriptions of their professional societies or registration Acts. Depending on local conditions these may be enforceable. Each paediatric speciality and sub-speciality may also have requirements, guidelines, and resources.
and resources. Investigators are urged to consult these at an early stage. Investigators should also satisfy themselves that they and their team members are meeting relevant professional obligations in addition to prescribed regulations, as the conduct of some assessment, intervention or outcome measure procedures may require a registered or accredited practitioner. Examples of professional societies that have guidelines for research are: the Royal College of Paediatrics and Child Health [26]; the European Academy of Paediatrics (formerly the Confederation of European Specialists in Paediatrics) [27] that provides guidance ranging from official statements to commentaries and summary presentations, for example that provided by Burt [28]; and the American Academy of Pediatrics [3]. Profession and subspecialty specific guides must be sought out by investigators to inform trial decisions if none exist, this should be noted somewhere in trial planning records so that the due diligence of trial leaders in this regard can be noted.

There are also guidelines from esteemed practice and research institutes that could be considered and used as methodological sources in trial plans. One is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This organisation has produced many resources including the oft-cited, *Guideline for Good Clinical Practice* E6 (R1) [29] which applies to the conduct of clinical trials, including essential documentation and archive guidelines; and the guideline for *Clinical Investigation of Medicinal Products in the Pediatric Population* E11 [30], that contains a series of guidelines for drug development and registration processes. These supplement more general ethical guidelines for biomedical research [31]. The Medical Research Council [7] provides an ethics guide for *Medical Research Involving Children* that clearly summarizes key points unique to paediatric trials. Guidelines for international research [31], and research involving human participants in developing societies may also be relevant to investigators working across international boundaries.

Guidelines from esteemed bodies can relate to particular paediatric populations and sub-specialties. For example, the Society for Adolescent Medicine has issued *Guidelines for Adolescent Health Research* [32]. Others such as the National Institute for Clinical Excellence (NICE) (http://www.nice.org.uk/) provide specialist resources on “best practice” approaches that can be incorporated into research protocols and general care of young people. While NICE guidelines cover public health, health technologies (including medicines, treatments and procedures) and clinical practice (for specific diseases and conditions) applicable within the National Health Service of the United Kingdom, they are useful practice benchmarks. Examples of approved guidelines include: *Improving Outcomes with Children and Young People with Cancer* [33] and *Feverish Illness in Children—Assessment and Initial Management in Children Younger than 5 years* [34]. Other guideline projects are underway for children. For example, *Prevention of Unintentional Injury in Children under 15* (due April 2010) and *Guidance on Looked After Children* (due September 2010). While there are no obligations on researchers to observe these guidelines in trial plans, they are useful practice benchmarks which may be required when arguing the case for equipoise in intervention or control groups.

In addition to professional society and advisory bodies, there are industry developed guidelines and issues papers. One example is the Association of the British Pharmaceutical Industry publication *Current Issues in Paediatric Clinical Trials* [35]
that reported on a conference covering matters such as regulation, ethics, parental perspectives, national frameworks and the industry perspective.

10.11.7 INSTITUTIONAL REVIEW BOARDS

Institutional review boards are often referred to in regulation as the local means to assess, approve and monitor studies. New investigators generally focus their approval efforts on these local bodies, and may not initially be aware of the recommendations, guidelines, regulations and conventions referred to earlier. Paediatric trial investigators should, however, set their views beyond local board requirements. A local compliance approach that breaches standards set in conventions or benchmark regulations may not be considered “reasonable” or “just” in the mind of the public or the law if a trial goes awry.

Notwithstanding the need for a broad view by investigators, many local boards are subject to regulations and guidelines at a national level and this may make local compliance adequate. For example in Australia, Human Research Ethics Committees are established through a formal process involving registration with the Australian National Health and Medical Council. Their conduct and reporting lines are mandated. In another example, local Institutional Review Boards in the U.S. have limits to their approval authority indicated by the level of risk and benefit incurred by research participants [14, 36]. So in some areas, there may be natural links from local boards to national regulations and international conventions, but this should not be assumed.

Institutional review boards that consider and approve paediatric trial research need to ensure that they have access to appropriate expertise to make informed decisions about research with youngsters. Local boards that approve paediatric research may later be on the defensive if problems arise and they did not have adequate paediatric expertise in place to make their decisions robust. Barrett [11] for example, suggests that research ethics committees should have members with practical experience in working with sick children so that they can assess whether or not risks to young participants are acceptable, protocols are workable, opportunities are provided for children to withdraw, and whether their autonomy is respected. Ethics committees also need to consider whether the research team has the paediatric capacity to do the study. Drawing on ICH [30], Kurz and Gill [38] recommend that paediatric trials should be done by “medical and scientific personnel who are familiar with GCP [good clinical practice] guidelines and are capable of a trusting relationship and communication with the child and parents … in … a child-friendly atmosphere with a paediatric infrastructure and personnel” (p. 43).

While ethics committees can interrogate researcher profiles as part of the approval process, local boards may make assumptions based on researcher reputation that is not backed up by documentation in the applications. This can easily happen if the researcher is a local who is well known for their expertise, or if a leading international researcher is involved and local boards do not feel comfortable interrogating his or her expertise. This can create later problems for boards if the appropriateness of the decision to approve research is challenged and the grounds for the decision about researcher capacity were scant. Paediatric investigators should therefore take some care in preparing the expertise statement that most institutional review board
the local means to focus their approval recommendations. A local decision or benchmark in the mind of the public may make local boards have the Ethics Committee with the approval of the reporting lines. In the U.S., there are benefit and natural links from ethnic issues, but this should be part of the ethical pediatric research to make informed approve pediatric research. They did not have robust. Barre1 [38] have members who can assess whether workable, opportunity and anonymity is respected. Earn has the pediatric illness [38] recommends personnel who are capable of a trusting... a child-friendly... 43).

part of the approval of a reputation that usually happen if the leading interpretable interrogating the appropriate patients for the database could therefore traditional review boards.

applications require. It may be worthwhile to detail pediatric clinical, professional, and research expertise relevant to the study topic, and to demonstrate that, between all team members, there is capacity for all study demands. In Australia, many institutions also require risk assessment prior to or following institutional review board approval for trial insurance purposes. It is not uncommon, for example, for subject and/or study-specific insurance to be required by some institutions for invasive clinical trials. The risk assessment outcome may depend upon the demonstrated pediatric research capacity of the investigation team.

10.11.8 TRIAL QUESTIONS

Trial questions need to be worthwhile and ethical. They need to be “honest and valid” [39, p. 836]. The technical skills involved in the development of trial research questions have been covered elsewhere in this handbook, as have the general ethical principles of beneficence, malefice and clinical equipoise, so this discussion will explore what principles underpin a worthwhile ethical pediatric trial question.

Pediatric clinical trials ask questions about the safety and efficacy of interventions for infants, children or youth. Kurz and Gill [38] proposed that pediatric research should therefore focus on the knowledge, cure, relief, or prevention of diseases of children. Biomedical studies must be devoted to reducing suffering and improving the prognosis of diseases” (pp. 42-43). To do this ethically, questions need to meet tests of relevance, benefit, originality, achievability, timing, and minimal harm. These are now explored.

The first issue facing investigators is whether or not the question is relevant to children and thus whether the involvement of young participants is essential rather than desirable. A high threshold needs to be met in this regard. The Royal College of Paediatrics and Child Health [26] identifies that research should only be conducted in children if the question cannot be answered by studying adults. Further, it identifies that involvement of children in clinical research will be required when an illness or condition only occurs in children, or has features that are more pronounced or have greater impact in young people. In such instances, research will be needed if there is no treatment information available or when what is known is inadequate. Paediatric research participation will also be required if the condition is in the general population but there is no paediatric treatment or there is only adult intervention evidence available [26]. Generally, paediatric inferences should not be drawn from adult studies, although occasionally it will have a long history of use in children that initially relied on adult data but has subsequently been complemented by consensus expert paediatric opinion [26]. In such instances, the weight of consensus expert opinion may mean that an exception can be made and a paediatric inference can be drawn. The Medical Research Council [7] provides five questions for researchers to help determine whether or not the involvement of children is essential or whether findings from adult studies would be adequate. These questions cover [7]: age specificity, developmental understanding, implications for pharmacokinetics, applicability of adult-style therapy and issues of later life disease prevention.

The second issue facing investigators is whether or not answers to the trial question will benefit children. Benefit to children is essential [30]. The Royal College of
Paediatrics and Child Health [26] identifies that paediatric research must not only be well designed and well conducted but it must have a real prospect of benefiting children. Benefits to children may be direct through trial participation in treatment or control groups or indirectly to children in general—even though there may not be benefits to individual trial participants. Benefit needs to be self-evident in the trial question and study description [40]. The Royal College of Paediatricians proposed that the following issues help make potential benefits to children clear [26]: magnitude of the condition including severity, how common it is and how findings will be used; how probable it is that research will achieve aims; who specifically will benefit from the research (whether it is child participants or children in general); whether benefit to children will be limited because treatment is expensive or hard to deliver; the type of intervention and whether a less invasive one could be used; the timing of benefits in terms of duration or later impact; and finally the whether the range of child participants is adequate in terms of potential benefits [26].

One simple way for investigators to consider benefit is to imagine that the study is finished, the trial question has been answered, then adopt the perspective of a public health official, a general practitioner, a parent or a child and ask “so what?”. What material benefit to children would accrue from the result? Does it merely confirm something already known? Is it interesting but not essential for child health and care? Is there any reasonable likelihood of direct benefit to participants or benefit to children in general? What would the “reasonable person” think about the study if they also knew the costs, risks and demands made on health care staff, participants and families to get the answer? Would the reasonable person agree that some children need to be exposed to risk to benefit children at large? Would the lay-person feel as Smyth [41] does that “we are all aware of the dramatic impact which results of clinical trials have had on the care and survival of children” (p. 838), and “there is an energy and dynamism which is both exciting and invigorating for paediatric clinical research” (p. 837).

While common sense, careful scholarship and the “so what?” test suffice for many trials, some studies and teams may benefit from involving ethicists in early stages of question development to ensure that a careful and considered approach to justice and benefit is taken. This is particularly important when trial interventions or measures may involve discomfort, distress or pain; or where the illness or condition brings inherent suffering or risk of death that may be exacerbated or alleviated by trial processes. A clear and scholarly beginning position on the issue of benefit to children not only helps investigators ensure their trial question is child-centred, but it also helps sponsors and participating institutions monitor progress of the trial and develop public and stakeholder communication plans.

The third challenge for investigators is to ask a question that can actually be answered. Is it achievable? Is it a question that the investigation team has the capacity to answer from the point of view of expertise, population access, resources and infrastructure? A question may not be realistic if there are insufficient potential participants for the study time frame; if the testing regimen is not physically or emotionally tolerable, or fails to accommodate family routines or responses; if sufficient funding, expertise, infrastructure or consumables are not guaranteed; if a-priori protocols for intervention, child care and data analysis are not transparent or cannot be adhered to; or if the findings are not going to be available or disseminated in ways that will grow the knowledge base to benefit children in general.
One of the most important issues to consider in weighing up whether a trial is achievable is the capacity of the team. Clinical proficiency and research skill is not enough—the team as a whole needs to have the expertise to conduct aspects of the trial. This may mean investigators must expand team membership to fill skill, knowledge and labour gaps that range from statistical analysis, ethical design, budget management, regulation compliance, use of clinical procedures and interpretation of findings and writing. Clinical professionals new to research sometimes learn the hard way that a good research idea is not necessarily a question that can be investigated. Alternatively these researchers don’t learn, they don’t use structural and capacity building strategies to get the study done, and instead they blame anyone involved in or connected to the project! The experience can leave clinical staff, managers, families, patients and researchers themselves disillusioned about the research experience and sometimes about each other. This is a particular risk for professionals who are attempting trial research in environments where they are already overloaded with clinical responsibilities and have limited prior experience of the technical and time demands of trials.

Turning a good idea into an achievable question requires a combination of scholarly, managerial and political skill that almost always involves long term collaboration of multidisciplinary experts. It almost never involves the "deity-like-researcher" funding followers or directing an operational team from a geographical or organisational distance. Such studies have inherent structural risks that make them prone to mistakes. Successful paediatric trials are always a team effort. They always involve the building of relationships over time with trust, respect and recognition. They always take effort on the part of the research leader to build and maintain a climate of open scholarly enquiry. Without such effort, mistakes may not be reported, good may leave, people fear betrayal or theft of their ideas or reputations, team failures rather than child participation can absorb emotional energy and the high cost of ethical practice required in the moral context of paediatric practice is understood. For paediatric researcher leaders there is, quite simply, no way to “delegate” a paediatric trial. Senior investigators must be involved in every aspect of trial planning, conduct, interpretation and writing as directors, collaborators or hands-on players. To do anything else is to risk allegations of being “front-men” or “poster girls” for trial sponsors, research institutes, or servants of their own “brilliant” centers—even when this is not true.

In addition to issues of team capacity, achievable questions rely on practical details such as estimating whether or not required sample sizes are attainable given the incidence of the condition, the recruitment target population, recruitment methods and time available. Many paediatric populations are very small, hard to access, and may have high decline rates in recruitment. Trial planners may need more than epidemiological data to estimate whether or not they have a reasonable likelihood of recruiting the needed sample—they may need local “on-the-ground” informants who can estimate the impact of recruitment methods on limited potential participants. The target sample size must not only account for the clinical effect size of the intervention in question but also appropriately deal with the confounding variable of developmental maturation, and practical issues such as likely decline rates and drop outs. Trial questions that require good luck to achieve sample sizes should be put to one side. This is hard for researchers to do, particularly if the question is their passion, however it must be done. Underpowered trial findings can
be worse than no findings at all—they give the illusion of reliable evidence. They are all too common in paediatric research. A review of trials published in the Archives of Disease in Childhood from 1982 to 1996, found that half the trials had 40 participants or less, which in the case of the trials reviewed meant that they were often under-powered [42]. Researchers should ask themselves “what is the point if an adequate sample size cannot be assured. Their attention should turn to more realistic questions or less rigorous research designs.

The fourth challenge for investigators is to ensure that the trial question is new. Questions should not be asked when answers are already known. The case of originality should be made clear in “study rationale” sections of institutional review board and investigation plan applications. The case for originality must be strongly set out, and as a research design. The strength of evidence should be compelling: systematic reviews, when rigorously conducted, provide a strong evidence base to demonstrate gaps or failings in current knowledge that can be used to justify originality.

Fifth, investigators need to be confident about the timing of trials that involve children—they should only be done when the knowledge base is “ready”. The nature of the trial should have a good fit with knowledge already available. ICH guidelines suggest [29, 30]: Phase 1 or 2 paediatric trials are acceptable only when disease being targeted are entirely or predominantly found in children; phase 2 or 3 trials are acceptable in children for serious conditions where no adequate treatment exits but only after safety and tolerability information has been gained from adult studies; and, Phase 2 or 3 paediatric trials are acceptable for conditions in the general population after there has been considerable research work in adults [29, 30].

Finally, trial questions need to balance anticipated harm with expected benefit and harm should be of “minimal risk”. Minimal risk can denote the type of procedure for data collection or intervention where only “very slight or temporary negative impact” might occur [7, p. 15], or where the risk is about the same as that in daily life, or with comparable treatments. Under regulation, potential risk to research participants must be identified and minimized and the prospect of direct benefit to research participants must be maximized.的风险在this instance refer to “any harm including physical injury, pain, distress, psychological harm, social economic or legal harms that might occur of physical injury occurs, or the potential harms that may be caused if research related information is shared with others [43]. This places heavy obligations on investigators to identify and describe what potential risks might be. The Royal College Paediatrics and Child Health [26] provides a guide to likely harm description by identifying five aspects to consider: the magnitude of severity; the probability of harms occurring; whether the type of intervention is invasive or non-invasive including psychological procedures; the timing of potential harm in terms of immediate duration or later effects; and finally issues of equity relating to the overuse of children who have many medical problems and are used in research because they are more easily accessible. In assessing harm control intervention and placebo conditions need to be considered—even placebos may cause harm—antihypertensive drug studies is a good case in point as this raises ethical issues regarding consent and trial design for a condition known to cause harm if left untreated [44].

While there is a requirement to assess likely risk, there is also an obligation to minimize whatever harm must be done to answer the trial question. There needs to
able evidence. This is published in Table 11, and the trials have 11.24.3. They were 'what is the point should turn to another than' trial question is not mentions. The case of the institutional review board must show strong evidence should provide a strong evidence that can be used of trials that involve "ready". The national ICH guidelines only when data is available. The data treatment generated from adult studies in the general population [29, 30]. An unexpected benefit the type of procedures required and temporary may be the same as that in 11.3 potential risks the procedures. The prospect of direct harm, social risks, or the potential shared with others and describe what health [26] projects to consider the type of interventions; the timing of and finally issues of potential problems and assessing harm control even placebo may point as this risk on known to cause loss an obligation decision. There needs to

be an appropriate balance between the harm done and the benefit achieved: expected benefit must exceed recognizable risks [and] serious predictable risks should be avoided" (38, p. 43). These are subjective judgements that must be made by investigators, institutional review boards and families of participants. Some judgements are easy—effective treatment should not be withheld from child parents. Other decisions about design and procedures are harder. The National Academy of the Sciences [45] provides a guide that may be helpful: researchers should consider the potential for age-related risks of harm; whether or not children are really needed; screening for known vulnerabilities; how demanding the protocol adherence is and risks arising from this; the use of only necessary procedures to answer the question; use of rigorous research designs; use of existing knowledge to estimate likely type and magnitude of risks; inclusion of adverse event information in data collection and reports of findings; ensuring investigator research and paediatric capacity; assuring appropriateness of the research setting for children; inclusion of safety monitoring, emergency arrangements, stopping rules for discontinuation; having clear guidelines for data use; and a plan for secure archiving [45].

To estimate and minimize likely harm, investigators must describe the level of risk of an intervention or outcome measure procedure. Defining level of risk is, however, a fraught task. It is one that involves judgement because currently, risk assessment lacks an empirical standard even though risks are supposed to be quantified, quantified and compared [39]. Some paediatric leaders have identified the need for guidelines [46, 47], although the use of guidelines is not universally supported [48]. Inadequate though they are, investigators should thus consult whatever regulation guidelines underpin their institutional review board requirements and ensure they benchmark their risk rating to the relevant regulation using scientific evidence for support. If there is limited scientific evidence available, the National Academy of Sciences [45] guidelines provide a framework for researchers to describe, as best they can, their strategies to minimize harm.

Researchers should also be aware that risk perception varies from the lay-person to the expert. As Afshar et al. [39] suggest: "experts usually assess harm in terms of mortality or morbidity, while a lay person may perceive harm in terms of severity, reversibility, the effect on future generations or influence on personal life. The main consideration should be the acceptability to non-experts, which in pediatric research are parents and older children. The most direct way of determining risk acceptability is to inform participants of the probability and magnitude of harm, and ask them about their preference" (p. 837). Whether or not the risk, discomfort and suffering caused is ultimately reasonable will depend on the question, interests of the child, preferences of the parents, likely benefit and comparison to likely harm in usual clinical practice.

10.11.9 PARTICIPANT CHARACTERISTICS

Infants, children and youth have unique body system and social attributes that need to be considered in trial research. Probably one of the most quoted phrases in pediatric research that emphasizes their unique position comes from the Royal College of Paediatrics and Child Health [26]: children are "not small adults". While every trial will need to investigate participant characteristics relevant to the sub-specialty,