Report

SURVEY OF CURRENT GUIDANCE FOR CHILD HEALTH CLINICAL TRIALS

The *StaR Child Health* Project: Standards for Research with Children

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List of abbreviations

AGREE tool	Appraisal of Guidelines Research and Evaluation
ANHMRC	Australian National Health and Medical Research Council
BPCA	Best Pharmaceuticals for Children Act
CHRB	Convention on Human Rights and Biomedicine
CIOMS	Council for International Organizations of Medical Sciences
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act (FDAMA)
FIP	International Pharmaceutical Federation;
GCP	Good Clinical Practice
HCTPD	Health Canada Therapeutic Products Directorate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals
IRB	Institutional Review Board
JPMA	Japan Pharmaceutical Manufacturers Association
MCRN	Medicines for Children Research Network
MRC	Medical Research Council
NCB	National Children's Bureau;
NIH	National Institutes of Health
PD	Pharmacodynamics
PK	Pharmacokinetics
PICU	Pediatric Intensive Care Units
PIP	Pediatric Investigation Plan
PMSB	Pharmaceutical and Medical Safety Bureau
PPRTC	Pediatric Pharmacology and Therapeutics Research Consortium
PREA	Pediatric Research Equity Act
RACP	Royal Australasian College of Physicians
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomized Controlled Trial
SA	South Africa
StaR Child Health	Standards for Research with Children
TEDDY	Task-force in Europe for Drug Development for the Young
TC	Tri-Councils
UK	United Kingdom
UNESCO	United Nations Educational, Scientific and Cultural Organization
US	United States of America
WHO	World Health Organization
WMA	World Medical Association

The *StaR Child Health* project: Standards for Research with Children

StaR Child Health is a new quality improvement initiative that seeks to enhance the quality, ethics and reliability of pediatric clinical research by promoting the use of uniform standards for clinical trials with children.

This goal will be achieved through

- raising awareness of the crucial importance of state of the art research design, conduct, and reporting;
- assisting in the development, dissemination and implementation of standards for research with children;
- becoming a global centre providing resources and training relating to the design, conduct, and reporting of clinical research with children;
- conducting empirical research relating quality, ethics and reliability of pediatric clinical research to the international standards for design, conduct and reporting.

StaR Child Health is directed by an international Executive Group that brings together leading experts in pediatric clinical research methodology and conduct from Canada, the Netherlands, Australia and the United Kingdom.

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Executive summary

At present, between 50 and 90% of daily prescriptions for sick children use ‘off label’ drugs. Recently, legislations were introduced to stimulate the pharmaceutical industry to investigate the pharmacological effect and safety of both new and existing medicines in children. The quality of pediatric randomized controlled trials is often suboptimal, in part because guidance for their design and execution is lacking. Also, evidence indicates that the quality of reporting of randomized controlled trials is less than optimal. The aim of this survey is to identify, classify, and appraise existing guidance on the design, conduct and reporting of pediatric clinical trials.

We systematically reviewed all relevant methodological and regulatory literature on standards or guidelines for clinical drug trials in children, over the period 1999-2009. The descriptives and contents of these guidelines were extracted and their quality was appraised by a modified version of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument.

Of 60 documents found on the internet and 3779 articles found in bibliographic databases, 22 internet guideline documents and 18 scientific publications which addressed recommendations for pediatric clinical trials were selected. The appraisal of these guidelines showed that the methods of research guideline development were poorly described. Areas of pediatric research that were addressed varied greatly and empirical evidence for recommendations was scarce. Most research guidelines are limited to “what one should aim to do” instead of “how to do it”.

There is a need for readily accessible, clear guidelines on how to design, conduct and report clinical drug trials in children in a scientifically valid and ethical way. To enhance their acceptance, these guidelines should be developed using transparent methods with input from investigators, regulators, WHO, and the pharmaceutical industry. Parallel to their development attention should be paid to their active promotion, implementation, and evaluation.

Introduction

1. Need for clinical trials in children

At present, between 50 and 90% of daily prescriptions for sick children use 'off label' drugs, agents that have not been tested for safety and efficacy in this population.[1;2] Examples include: proton pump inhibitors which have limited indications for children but no suitable dosage form; phytomenadione for partial reversal of warfarin therapy; treatment or prophylaxis with low molecular weight heparin for thrombosis; antihypertensive medicines; clonidine for sedation in Pediatric Intensive Care Units (PICUs) and melatonin for sleep disturbance. Consequently, there is insufficient information about dosage, safety and efficacy. This means that child health care providers lack the basic scientific data that they need to be able to make informed judgments for their patients, a situation that is considered unacceptable for adults. Indeed, an increased risk of adverse drug reactions and ineffectiveness of particular drugs have been demonstrated, due to the use of off-label or unlicensed drugs in children.[3;4]

Extrapolation of adult to child data is problematical for several reasons. Pharmacokinetic (PK) and pharmacodynamic (PD) processes in children differ considerably from those in adults. In addition, we have learned from developmental pharmacology that the pediatric population cannot be considered as a homogeneous group. Different age-groups that have their own PK- and PD-particularities have been defined: "preterm and term neonates" from 0 to 27 days, "infants" from 1 to 23 months, "pre-school children" from 2 to 5 years, "school children" from 6 to 11 years and "adolescents" from 12 up to 18 years.[5] The safety and efficacy of drugs is development-dependent. Therefore, clinical trials are needed that investigate optimal dosages and formulations in various pediatric age groups.

2. Challenges in clinical trials in children

There are several reasons why only few clinical trials have been performed in children. Compared to adults, children are generally prescribed fewer drugs for a shorter period. The high development costs and limited expected gain of new pediatric drugs pose a major disincentive for the pharmaceutical industry. Additionally, the limited number of eligible trial subjects yields its own practical problems, such as inadequately powered studies and inability to demonstrate moderate but clinically relevant treatment effects.[6] This problem is expanded by the heterogeneity of the pediatric population and thus the requirement of stratification according to age-group. Furthermore, recruitment is difficult in pediatric research,[7;8] which is related to the limited number of children with specific diseases, fear or inconvenience of parents to let their child participate, and strict inclusion and exclusion criteria.

Ethical concerns about the inclusion of children in clinical trials are widely acknowledged,[9] and much has been written about this subject (see Appendix 1). In 1979, the Belmont report was the first to recommended special protection for vulnerable populations, including children, in research.[10] The Declaration of Helsinki states the need for written informed consent of the subject or proxy consent from a legally authorized representative of a child.[11] Informed consent and assent procedures and the requirements for this are more complicated than in adults because they depend on age and level of development of the child. Therefore, different laws and ethical "guidelines" were developed over the years, which also addressed

pediatric issues such as the requirement of minimal burden, the wish for an optimal harm/benefit balance and special attention for the varying ability of children to understand and adequately interpret the consequences of participation.[10-23]

PK and PD studies in children yield their own challenges,[8] such as the need for different formulations, administration and dosing strategies, adherence issues, the limited possible number and volume of blood samples in small children and the influence of growth, maturation and development on adsorption, distribution, metabolism and excretion. Finally, the lack of validated age-appropriate (pharmacodynamic) outcome measures often limits the interpretation of the results.

3. Recent Developments

Despite these challenges, the need for the appropriate investigation of drugs in children is now recognized worldwide. In recent years there has been an important shift in opinion, both in the United States (US) and the European Union (EU), about conducting clinical trials involving children. Acquiescence in the current unsatisfactory situation is no longer regarded as tenable and the lack of drug trials in children is now seen as a major ethical problem. Therefore, the US and the EU have introduced incentives and legislations to both stimulate and force the pharmaceutical industry to investigate the pharmacological effect and safety of both new and existing medicines in children (see Appendix 2). This legislation was meant to lead to an increase in studies into medicines for children.

In the US, legislation on pediatric drug research has gradually been introduced since 1997. First, the Food and Drug Administration Modernization Act (FDAMA) provided financial incentives, by granting an additional period of 6 months of marketing exclusivity if a pharmaceutical company conducted and submitted pediatric studies of a medication (Pediatric Exclusivity Provision).[24] On the other hand, the Pediatric Rule of the FDA was introduced, which required drugs for new therapies and indications to be studied in children.[25] Additionally, the US National Institutes of Health (NIH) issued a policy that required inclusion of children in all human subject research conducted or supported by the NIH, unless there were scientific or ethical reasons to exclude them.[26] Although these first regulations have resulted in some success, in a number of important children's diseases trials were still not conducted because of insufficient financial incentives. For this reason, a legal obligation has been introduced in the US for companies to conduct trials with drugs for children where there is a therapeutic need, the Better Pharmaceuticals for Children Act (BPCA) 2002.[27] It provides financial incentives to companies to undertake clinical trials to improve safety and efficacy of products used in the treatment of children whilst the products are still "patent protected". The Act also provides for research on older off-patent medicines through a priority list developed by the NIH.[24;27] The Pediatric Rule was succeeded by the Pediatric Research Equity Act (PREA, 2003), which enables the FDA to request pediatric data in studies on drugs and biologicals.[28] Finally, the BPCA and PREA were adapted in 2007.[29]

Meanwhile, the European Parliament issued Directive 2001/20/EC, which provided a detailed framework for the conduct of clinical trials, and stated that drugs that will be used in children should be tested in clinical trials in the target age group.[17] In 2007, "the Regulation of the European Parliament and of the Council on Medicinal Products for Paediatric Use" (Regulation No. 1901/2006 and amendment 1902/2006) was introduced.[30] This has established a system of requirements and incentives aimed at satisfying the need for ethically researched drugs that are appropriately formulated and authorized for the treatment of children. The European regulator, EMEA, now requires the approval of a pediatric investigation plan (PIP) for every application for a new therapeutic agent.

Because EMEA also regulates drug research in Australasia (excluding Japan) and other parts of the world, these regulations have widespread implications. EMEA has developed a "Priority List" to ensure that funding provided through the EU Framework programmes is directed into research of medicinal products with the highest need in the pediatric population.[31] In addition, all clinical trials are registered in the central EudraCT database.

In Japan, which has its own drugs regulator, there are currently no laws or regulations that require pediatric studies for approval of drugs.[32] Similarly to the rest of the world, very few drug products are indicated for use in children, but drug studies in children are encouraged by the Ministry of Health and Welfare.

Encouraged by new regulations and incentives, (inter)national scientific organizations and academia have also recognized the need for better drug trials in children. This has resulted in the foundation of national pediatric research networks in Europe. A Medicines for Children Research Network (MRCN) was established in the United Kingdom (UK), Finland, Germany, France, and the Netherlands. A European network initiative is the Task-force in Europe for Drug Development for the Young (TEDDY), while in the US the NIH now solicits grant applications to create a Pediatric Pharmacology and Therapeutics Research Consortium (PPTRC).

The need for better medicines for children also applies to developing countries, where an estimated 10 million children die every year, from causes such as diarrhoea, malaria, respiratory tract infection, pneumonia or HIV/AIDS. Although approved drugs exist for these diseases, additional problems in these countries are the costs and problems with distribution and storage. The World Health Organization (WHO) has launched a global campaign 'make medicines child size' spearheaded in December 2007 to raise awareness and accelerate action to address the need for improved availability and access to safe child-specific medicines for all children under 15 years of age. WHO recognizes that to achieve this goal, more research is needed, more medicines need to be developed, and improved access measures are essential. WHO developed an essential medicines list for children, which attempts to specify the available proper pediatric dosages and formulations.[33]

Yet, performing pediatric drug trials in developing countries has even more challenges than discussed above. The performance of high-quality trials with close monitoring, for example, will not always be feasible. While in developed countries much has been written about the informed consent procedure in children, these rules are difficult to implement in developing countries. Perhaps even the main challenge is to encourage pharmaceutical industries to perform expensive and often difficult pediatric drug trials, for a market with very limited resources.

4. The need for scientific standards

The recent developments are expected to result in an increased number of pediatric clinical trials. However, evidence indicates that the quality of reporting of randomized, controlled trials (RCTs) is less than optimal.[34] Methodological analyses indicate that inadequate design and reporting are associated with biased estimates of treatment effects. Yet, especially in a vulnerable population such as children, it is essential to conduct scientifically valid research. Therefore, the incentives for more trials should be accompanied by readily accessible information on how to design, conduct and report pediatric clinical trials. This information should be provided in guidance that is developed to encourage and facilitate timely pediatric medicinal product development internationally. Such guidance should cover critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of drugs in the pediatric population, anywhere in the world including developing countries.

Objectives

The first step in the development of uniform standards for the design, conduct and reporting of research with children is to identify all available standards thus far. The question arises: is there good quality guidance for pediatric drug trials?

Consequently, the main objective of this survey is to systematically review all published methodological and regulatory literature defining standards or guidelines for clinical trials in children.

After selecting possible relevant guidelines we

1. Discuss the scope of the various different guidelines;
2. Critically appraise the quality of these guidelines;
3. Identify and classify areas in which guidelines are needed.

Methods

1. Search strategies

We performed an extensive literature search with the aim to identify all documents describing guidelines or standards for the design, conduct and reporting of clinical drug trials in child health. A literature search was done using Medline, Embase and the Cochrane Central Register of controlled trials (issue 1, 2009). The Medline, Embase and Central search strategies are presented in Appendix 3. Secondly, we searched the general internet through a Google search (including a search for textbooks) and we screened professional websites of (inter)national pediatric networks, regulatory authorities and scientific organizations (Appendix 4).

Only documents published in the past 10 years (Feb 1999-Feb 2009) were included, because regulations have changed during the last decade. Since we used English search items, this search mainly yielded guidelines from English-speaking countries. No language restriction was used for this particular search. Reference lists of relevant documents and personal collections of papers of all members of the *StaR Child Health* working group were screened for additional documents.

To identify guidelines we searched the general internet with the following text words: *guidance, standards, consensus, recommendations, checklist, requirements, instructions* or *policy*. In this review we will use the term guidelines to describe all these terms. The MESH definition for guideline is "… a work consisting of a set of statements, directions, or principles presenting current or future rules or policy". Guidelines may be developed by government agencies at any level, institutions, organizations such as professional societies or governing boards, or by the convening of expert panels. We defined a standard as "a set of guidelines established by one or more persons using a recognized transparent approach either based on empirical evidence or consensus of experts". No limitation for the method of guideline

development was used. Consensus and regulatory documents as well as scientific reports were included.

2. Study selection

We identified two types of guideline publications: 1) scientific publications in medical databases and 2) documents retrieved by our general internet search which were qualified as *directive, recommendation* or *guideline* (further referred to as “internet guidelines”). Two reviewers (FF, JL) independently selected relevant articles published in the last ten years by the following criteria: making recommendations (1) for the design, conduct or reporting of clinical trials (2) in children aged ≤ 18 yrs (3). Official laws and regulations were excluded. Disagreements were resolved in a consensus meeting.

3. Data extraction

3.1. Descriptives of guidelines

Three reviewers (FF, JL, JU) independently extracted descriptive information from each selected document, including title, authors and institutions, country of development, year of publication and update, scope, objective(s), patient groups addressed and target users. For this purpose, a data extraction form was developed, which was piloted by two members of the *Star Child Health* group (JL, JU).

3.2. Contents of guidelines

To systematically extract the contents of the different guidelines, three reviewers (FF, JL, JU) developed a list including all items that are of importance in the design, conduct and reporting of pediatric drug trials during the selection process. The list was based on the items that were addressed in the ICH E11 document ‘Clinical investigation of medicinal products in the pediatric population E11’ and complemented with all items that were subject of the screened full text publications, items previously collected for the *Star Child Health* project and items that were addressed in other retrieved guidelines. Then, the three reviewers classified these items into eight (8) different domains. Three methods to validate this process and to complete the list were used. First, the list was piloted on four guidelines by three reviewers. Secondly, the list was sent out for consultation and approval to all members of the *Star Child Health* development group and finally, additional items could be added by the reviewers during the data extraction process. Identified areas were: *ethics, design, practical issues, procedures, pharmacology, outcomes, statistics,* and *reporting*. Disagreements were resolved in a consensus meeting.

We systematically extracted the content of all documents that were qualified as an internet guideline, using the above mentioned list. Due to the large number of guidelines and guideline items, it was not feasible to extensively describe what each guideline recommended on each specific item. Instead, the list can be used to identify which guidelines address specific areas or items. Because most scientific publications either addressed just one specific item or consisted of a very limited number of specific recommendations concerning one domain, only a brief overview of the domain that was addressed is given.

3.3. Quality appraisal process

The three reviewers systematically assessed the retrieved guidelines using an adapted version of the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument (http://www.agreecollaboration.org). The original AGREE instrument is designed to assess the process and reporting of clinical practice guideline development. It consists of 23 items within 6 domains, each intended to capture a separate dimension of guideline quality. We excluded 9 of the 23 items because they were only applicable to clinical practice guidelines and not to guidelines concerning the design, conduct and reporting of clinical research in children (see Appendix 5). Each item was scored with “yes”, “no” or “unknown”. It is important to keep in mind that there is no validated instrument available to assess the quality of guidelines for research. Moreover, the AGREE instrument places much emphasis on the reporting of the development process. Therefore, rigorously developed guidelines may score poorly when the methods used to develop the guideline are not well described.

Results

In total, 18 scientific publications and 22 internet guidelines satisfied all our inclusion criteria. The scientific publications were either qualified as a guideline or consisted of a general text on pediatric clinical drug trials which included specified recommendations within the text. These were mostly written by investigators and clinicians, while the internet guidelines were written by (international) scientific organizations, regulators or governments. Since most scientific publications either addressed only one specific item or consisted of a very limited number of specific recommendations concerning one domain, a brief description of each publication is given, including a short summary of the scope of the guideline, but not the exact content, nor a quality assessment. In contrast, the content and quality of all the internet guidelines will be described below.

1. Description of scientific publications

The literature search yielded 3779 publications. Of these, 3513 publications were excluded on the basis of title and abstract. Mostly, these were clinical trial reports of specific drugs tested in children. Of the 266 publications of which the full text was retrieved, 15 were included because they consisted of recommendations for the design, conduct or reporting of clinical trials in children. In addition, three actual guidelines on the design, conduct or reporting of clinical trials in children were found by reviewing the references of the retrieved publications. The descriptives of these 18 scientific publications[16;20;35-50] are summarized in Appendix 6. Thirteen reports concerned children of all ages. The remaining five reports addressed specific age groups[36;46;47] or children with specific diseases.[41;50] Four reports addressed multiple aspects of pediatric clinical trial research.[35-38] Twelve reports gave recommendations on issues regarding ethical issues in pediatric clinical trials.[16;20;39-48] Three of these also addressed study design.[46-48]. Two additional reports addressed topics on pediatric study design[49;50], while none addressed practical issues, procedures, outcomes, statistics or reporting.

2. Description of internet guidelines

The general internet search resulted in 60 documents that potentially contained recommendations on the design, conduct or reporting of clinical trials in children. Three reviewers scanned the documents and selected 22 documents which fulfilled all inclusion

criteria (see Appendix 7a).[5;8;13;17-19;22;23;26;51-63] The documents that were excluded are listed in Appendix 7b. The general descriptives of the documents which were qualified as internet guideline are presented in Appendix 8a. The *European Clinical Trial Directive* addresses good clinical practice and ethics of conduct of clinical trials, including recommendations for children.[17]

The main document on children in clinical trials was the ICH E11 'Clinical investigation of medicinal products in the pediatric population E11'.[5] Both a Canadian addendum and a chapter on clinical trials in children from the only included textbook were based on this guideline.[8;54] Two additional guidelines on children in clinical trials were the NIH policy on participation of children in clinical research[26] and the FDA additional safeguards for children in clinical investigations[13]. Two guidelines addressed ethics in human research including a paragraph on children[18;51], while five gave recommendations specifically on ethics in pediatric research.[19;22;23;52;55]

The remaining nine guidelines addressed specific aspects of the design or conduct of clinical trials in children. Five documents discussed pharmacological aspects, i.e. pharmaceutical research[53], pharmacokinetics[57;63], pharmacovigilance[58], and formulations[62]. One guideline addressed the registration of pediatric clinical trials[56], one gave recommendations on clinical trials in small populations and two were applicable to specific subgroups, i.e. neonates[61] and children with cancer[60].

The guidelines were developed by regulatory authorities (EMEA: 6[57-62], FDA: 2[13;63]), (inter)national scientific organizations (Council for International Organizations of Medical Sciences (CIOMS)[18], the UK Medical Research Council[19], and the ICH[5]), pediatric networks (the task-force in Europe for drug development for the young (TEDDY)[55], the Royal Australasian college of physicians (RACP))[22], governmental organizations (EU 3[17;23;56], the US NIH[26], organizations from Australasia[51], Finland[52], and Canada[54]), and the international pharmaceutical federation (FIP)[53].

The composition of these development groups was poorly described. The main guideline "Clinical Investigation of Medicinal Products in the Pediatric Population" (ICH E11)[5] was adopted by the three main regulatory authorities, i.e. the FDA in the United States, the Pharmaceutical and Medical Safety Bureau (PMSB) in Japan and the EMEA in Europe and the rest of the world, including Australasia and Africa.[64-67]

Target users were poorly described, but target users that were mentioned in guidelines were: investigators, clinicians, applicants, regulatory authorities, institutional review boards (IRBs), policy-makers, advisory councils, industry, patients and the public.

3. Contents of internet guidelines

The contents of the internet guidelines are summarized in Appendix 8b. We scored whether the different domains and items relevant for the design, conduct and reporting of clinical trials in children were addressed in each guideline.

One document discussed the conduct of clinical trials in small populations[59] and 3 were general guidelines on clinical trials that addressed children in a special paragraph.[17;18;51] The patient groups of the remaining 18 documents were children in general (n=16) or specific subgroups, i.e. neonates[61] or children with cancer[60].

Ethics

The ethical domain was the most extensively addressed domain. Twenty out of 22 guidelines addressed ethical aspects of clinical research in children, while ethics was the main topic of 9

of these guidelines.[13;18;19;22;23;26;51;52;55] All applicable guidelines agreed that children can only be included in clinical trials when there is a positive benefit/risk balance. The interest of the study subject should prevail over those of science and society.

Risk assessment A careful risk assessment is required, taking into account aspects such as the burden of disease, the current standard treatment effects, intrusiveness of research and drug safety issues.[23] Risks may vary according to age. Different degrees of risk have been identified. In the US, “no greater than minimal risk” versus “greater than minimal risk and prospect of direct benefit” versus “greater than minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects” are defined.[13] The EU guidelines define “minimal risk” versus “minor increase over minimal risk” versus “greater than minor risk increase over minimal risk” categories.[23] From this sample it appears that, thus far, there is no consensus regarding the exact method of risk assessment. Yet, there is consensus that the burden of pediatric research, i.e. procedures associated with pain or distress, the impact on daily life, should be minimized.[5;8;13;17-19;22;23;51;52;55;61]

Informed consent and assent Children are unable to give legally binding consent, which makes the informed consent procedure of pediatric clinical trials complicated. The informed consent procedure was addressed in 16 guidelines. Informed consent for the inclusion in clinical trials must be given by the parent or legal representative on the child’s behalf. The child should give assent, but the ability to give assent depends on several factors, such as age, level of development, intellectual capacity, and disease experience.[23] Other child-specific aspects of the informed consent procedure are the requirement for written assent in older children, age-appropriate information sheets and privacy issues in adolescents. Age limits for assent were discussed in 10 guidelines. These limits differ between countries, but also between different IRBs within one country. Nine guidelines state that no financial rewards for parents or children are permitted, except for compensation of expenses or travelling.

Healthy pediatric volunteers The opinion on healthy pediatric volunteers varies, but according to the UK MRC it is ethical for a healthy child to participate in research as long as appropriate consent has been obtained, there is no more than minimal risk and the research is not in conflict with the child's interest.[8;18;19;23;52;54] Since children cannot give legal consent and young children cannot give assent, the use of placebo is more restricted than in adults. True equipoise is required. Placebo control is only deemed acceptable if there is no commonly accepted therapy, or the commonly used therapy is of questionable efficacy, or the commonly used therapy has a high frequency of side effects.[8] A similar problem is seen with the use of comparators, because many of the standard treatments for pediatric diseases have not been appropriately licensed. These aspects are discussed in seven guidelines.[8;18;19;23;52;54;55;59;61]

Role of Institutional Review Boards National, local or hospital-based IRBs are responsible for the review of pediatric clinical trials and their role was discussed in 14 guidelines. A problem is that their role differs per country and even within countries, leading to inconsistent responses to identical study requests. Other ethical aspects that were addressed in included guidelines, are the requirement of investigators trained in working with children[8;13;19;23;51;52;61] and the conduct of clinical trials in developing countries.[22;23]

Design

Eight guidelines considered the timing of pediatric trials.[5;8;23;53;54;58;60;61] This timing depends on the product, the type and severity of the disease being treated, the patients for whom the product is intended, safety considerations incorporating knowledge of preclinical and adult studies, and the availability, efficacy and safety of alternative treatments. Although a plan to study new drugs in children should be submitted during the early phases of drug development, the actual start of a pediatric trial will often be postponed to later stages,

sometimes even after a post-marketing period in adults. This in order to prevent children from needless exposure to compounds without benefit.[8] In general, initial safety and tolerability data are to be collected from adult studies first.[5]

Eight guidelines gave suggestions for possible alternative study designs.[5;8;19;23;57;59;61;63] Patient recruitment difficulties were discussed in four documents.[5;8;22;53] The importance of stratification for age (n=7)[5;8;53;57;58;60;61] or other factors (n=5)[5;57;59;61;63], such as disease severity, concomitant disease, weight and developmental level, is well recognized. Eleven guidelines described the various age subgroups that can be identified.[5;8;23;26;52;53;57;58;61-63] The age groups proposed by the ICH guideline (neonates, infants, children and adolescents) were used most often.[5]

Due to the limited number of children with specific diseases, multicenter studies are often preferred in pediatric research.[5;8;51]

Three guidelines mentioned eligibility issues in children.[5;8;60] Inclusion criteria should not be too strict in order to allow enough patients to enter a study[8] On the other hand, eligibility criteria such as adequate physiologic status are sometimes required, for instance to distinguish organ-specific toxicities from underlying organ dysfunction in phase 1 oncology trials.[60]

Multiple guidelines agree with the ICH E11 guideline statement that extrapolation from studies in adults or older children may be appropriate when a drug is to be used in children for the same indication as those studied and approved in adults, when the disease process is similar in adults and children, and when the outcome is likely to be comparable.[5] Then, PK studies in all the age ranges likely to receive the drug, together with safety data, may provide sufficient information. In neonates and infants, however, this is often not possible. Thirteen guidelines address these or other possibilities of information use from other studies.[5;8;17;19;23;53;54;57-63]

Post-marketing surveillance studies are important in children, because the study drug may influence the physical growth and cognitive development of a child and long-term adverse events must be anticipated.[5;8;53;58;60;61]

Another design/conduct issue that was addressed in two guidelines was the institution of a Data and Safety Monitoring Board (DSMB), in order to monitor the level of risk of a study and to give advice about early stopping of clinical trials.[23;51]

Practical issues

Only three guidelines addressed practical issues of clinical trials in children.[8;59;61] All three of them addressed logistical or infrastructural barriers, while the EMEA guideline on neonates[61] also discussed technical issues, such as the difficulties of blood sampling or drug administration in neonates. Examples of possible infrastructural improvements are the development of a robust pediatric clinical study infrastructure, including trained and experienced investigators and centers of excellence, and collaboration between the public and the private sector.[8] Although it is well-known that pediatric drug development is not financially attractive, only the textbook chapter on clinical trials in children briefly discusses why pediatric studies cost more than adult studies.[8]

Procedures

There is wide agreement that the volume and frequency of blood withdrawals should be minimized in children, especially in the younger ones.[5;8;19;23;52;57;61;63] Approaches that are used to this end comprise the use of sensitive assays, experienced laboratories, collection during routine blood sampling, the use of indwelling catheters.[5] Other interventions, especially invasive procedures, should also be restricted.[23;52;61;63]

Pharmacology
The pharmacology domain is very important in children, because growth, maturation and development affect pharmacokinetics (PK) and pharmacodynamics (PD), bioavailability, drug response, and dosing requirements. The FIP statement, the ICH E11 guideline as well as regulatory guidelines discuss the different pharmacologic aspects, including various pharmacokinetic study designs.[5;8;52;53;57;58;60-63] Due to differences in PK/PD, different dosing schemes are required according to age, based on weight or body surface area, which is addressed in nine guidelines.[5;52;53;57;58;60-63] The role of growth, maturation and development in pediatric pharmacology is discussed in eight guidelines.[5;8;54;56;57;61-63]

The ability to take drugs varies with age, therefore the development of multiple formulations and the development of different routes of administration is required.[62] Especially in young children, taste and smell will affect compliance. Not all excipients that are used for adult medications can be applied in medications for children.

Study outcomes
The requirement of different outcomes in trials in children as compared to adult trials, but also between children of specific ages is addressed in some, but not many guidelines.[5;8;19;57;61] Another topic which is scarcely discussed is the need to use measurement instruments that are adjusted for age and level of development, especially when measuring subjective symptoms such as pain.[5;8;57;61] On the other hand, almost all guidelines address pediatric clinical trial safety issues, both short and long-term.[5;8;17;19;22;23;51;53-55;57-61;63]

Children may suffer from adverse events that differ from those in adults and the influence of the drug on physical and cognitive growth and development should be investigated, especially because these effects may only be noticed at a later stage.[8] Various age groups may respond differently. Likewise, drug interactions and the effect of a drug may vary according to the developmental stage of the patient.[5;8;23;26;52;58;60;61]

Statistical methods
Eight guidelines describe different statistical methods that can be applied in pediatric drug research, e.g. statistics that can be used in small populations.[8;23;53;57-59;61;63] Population PK approaches and sparse sampling methods are interesting in children, because they can reduce the number of required blood samples.[5;23;57;61;63]

Reporting
All clinical trials that started in the European Union after 2004 have to be entered in the EudraCT database. In 2009 a guideline was developed which describes what information concerning pediatric clinical trials has to be entered into this database and what information has to be made public by the EMEA. The goal is to increase the availability of information on the use of drugs in the pediatric population and to avoid unnecessary replication of studies.[56] Examples of variables that should be recorded are: objectives, trial design, rationale for the study, trial population, outcome measures, recruitment, baseline data, (statistical) analysis and adverse events. This guideline also addresses the time frame of publication, whereas three other guidelines only address the requirement of publication.[19;22;23] The two Australian guidelines are the only guidelines that discuss the reporting of trial results to participants.[22;51]

Overall, the guidelines state “what one should aim to do” when designing or conducting a clinical trial in children, but hardly any guideline described “how to do it”. Empirical evidence that underpins the recommendations for the design and conduct of clinical trials in children is hardly ever discussed.

4. Quality appraisal of internet guidelines

The quality appraisal scores of the 22 guidelines are presented in Appendix 8c. Regarding the item 'scope and purpose', only 5 out of 22 guidelines specifically described both the objectives and patients to whom the guideline was meant to apply. Target users ('stakeholders') were defined in 12 out of 22 guidelines. The 'rigour of development' of all guidelines was judged very poor. Only 7 out of 22 guidelines described their development process, and to a very limited extent. Although seven points could be scored for this item, only two guidelines scored more than 1 point (maximum 3). Moreover, the 'clarity and presentation' as well as the 'applicability' also received low scores. None of the guidelines described (the lack of) a conflict of interest.

Discussion

In this report we systematically reviewed all published methodological and regulatory literature defining standards or guidelines for the design, conduct or reporting of clinical trials in children. Twenty-two relevant guidelines[5;8;13;17-19;22;23;26;51-63] were retrieved from websites of governments, scientific organizations and regulatory authorities. In addition, the medical database search yielded 18 publications containing recommendations[16;20;35-50] on how to design, conduct or report clinical trials in children. Three more guidelines were retrieved from the references of the retrieved publications.

Most internet guidelines discussed the ethics of clinical research in children, some addressed general aspects of clinical trials in children and the others described various issues in specific domains of the design or conduct of pediatric clinical trials, such as study design or pharmacology. Although some topics, e.g. ethics, were addressed extensively in several guidelines, other topics were hardly discussed, e.g. the need for stratification according to age, the use of child-specific outcomes and the requirement for reporting of the results. Moreover, guidance was predominantly aimed at what should be done, but guidance on how best to address these topics was virtually absent.

Since we included all guidelines that contained recommendations for clinical trials in children, different types of guidelines were retrieved. Apart from regulatory guidelines concerning different aspects of pediatric research, explanatory guidelines from governments and scientific organizations were found. These were often based on regulations or other existing guidelines, especially the ICH E11 guideline 'Clinical investigation of medicinal products in the pediatric population E11'.[5] The domain most extensively addressed was ethics. This is no surprise, because the relevance of this topic regarding research in children was the first to be recognized as early as in the seventies.[10;64] Ironically, ethical concerns were also the reason why pediatric research has been limited for a long time, which was the cause for the recent regulatory changes in the US and Europe.[21;27-30]

Although ethical guidelines[18;19;22;23;51;52;55] were numerous and their content sometimes contradictory, we found the recently developed comprehensive consensus guideline from the European Union.[23] This guidance is now adopted by EMEA and thus will have to be used in the design of future trials in Europe, Australasia and Africa. The only drawback of this guideline is the fact that we could not assess the level to which this guideline was evidence-based. References were given at the end of the text, but they were not directly connected to each topic in the text. Yet, research ethics remains more of a consensus topic than a topic that can be supported by empirical research.

Other topics than research ethics were addressed in guidelines on general aspects of pediatric clinical research[8;13;17;26;54] and guidelines that were specifically developed to give information on certain domains[53;56-58;60-63], such as pharmacology or trial registration. Items that were addressed by nearly half of the guidelines are the use of information from other studies, age classification (classified under "design" in this report), dosing or formulation adjustments, PK/PD issues (pharmacology), short and long-term safety, as well as the role of growth, maturation and development (outcomes). Items that were hardly addressed are recruitment of children, the need for stratification according to age or other factors, post-marketing surveillance studies (design), logistical and economical barriers (practical issues), the need for child- specific and age-specific outcome, including measurement instruments (outcome), and all items of the reporting domain.

The major problems of the guidelines included in this review are the following. First, the lack of empirical evidence for the recommendations. Second, the guidelines told 'what one should aim to do', but not 'how to do it'. And, third, the lack of transparency of the development process.

All the guidelines received very low quality scores on all the domains of our adapted version of the AGREE instrument. Although the AGREE instrument (http://www.agreecollaboration.org) was developed for assessing the quality of clinical practice guidelines and not for clinical research guidelines, 14 out of 23 items were applicable and relevant to both and could thus be used. Since this was the only known validated instrument to critically appraise medical guidelines, the use of an adapted version was preferred over the ad hoc development of a new quality scoring system. We knew in advance that the AGREE instrument places much emphasis on the reporting of the development process, leading to low quality scores when the development process was not well described. Although this applied to almost all guidelines, low scores were seen throughout all domains, not merely the rigor of development domain, implying that this was certainly not the only contributor to the low guideline quality. In contrast, this underscores the need for the development of new, high-quality guidelines regarding the design, conduct and reporting of pediatric clinical research. The development of a validated quality appraisal system for research guidelines may be part of this development. The need for critical appraisal of reporting guidelines was recently recognized by the Equator Network as well[68], but no instrument has been suggested thus far.

In contrast to the internet guidelines, the scientific publications often consisted of empirical research, but they only contained a limited number of recommendations. Most were specialized scientific publications on specific medical conditions, e.g. hypertension[50], or a well-defined age group, e.g. neonates[46]. Still, we believe these recommendations can be very useful in future guideline development.

Apart from the 18 included scientific publications, our medical database search retrieved many very interesting empirically based publications on different topics concerning pediatric research. However, these are not included in this report because they did not address these topics in the context of clinical trials, or they did not contain recommendations.

Not all relevant articles may have been retrieved by our search, because the search strategy was aimed at identifying published guidelines consisting of recommendations for pediatric clinical trials in general. Publications that addressed specific domains instead of clinical trials or publications that were not developed specifically for children may contain relevant information for the development of pediatric guidelines, but the retrieval of such guidelines was beyond the scope of this review. Examples are a guideline on pediatric dosing[69] and a publication on the impact of staged informed consent.[70] We consider our checklist of domains and items specific for pediatric research to be comprehensive, because it was thoroughly developed and approved by different experts in the field. The fact that few

additional items were encountered during the final data extraction process reinforces this notion that the list was fairly complete.

Recent regulatory changes are expected to lead to an increase in the number of clinical trials in children.[21;29;30] Especially in this vulnerable population, it is essential to conduct scientifically valid research. Therefore, the incentives for more trials should be accompanied by readily accessible information on how to design, conduct and report pediatric clinical trials. However, we found that little guidance is available and that the guidance that is available does not cover all relevant domains, nor is it based on empirical evidence. The development of widely acknowledged, uniform standards for research with children will prevent researchers from having to choose between numerous, sometimes conflicting , and occasionally contradictory guidelines.

The implementation of these guidelines should be applicable to developing countries as well, provided researchers from there are involved in the guideline development. The implementation of the results of high quality research will eventually enhance the use of safe and effective medications and prevent the use of ineffective interventions, inefficient use of scarce resources, and perhaps most importantly, harm to patients in developed as well as developing countries.[71;72] In the end, not only patients and their parents, but also pediatricians, researchers, regulatory authorities, buyers, and pharmaceutical industries will benefit.

To obtain the highest benefit of future guidelines, it is important to involve all the various different stakeholders in pediatric research, including investigators, pediatricians, regulatory authorities, reviewers of research, parent and patient organizations, funders and governmental organizations. The *StaR Child Health* group has been initiated to act as an international network, bringing together developers of pediatric research guidelines, medical journal editors, research funding bodies, and other key stakeholders with a mutual interest in improving the quality of pediatric research.

Conclusions

This systematic review of the literature highlights a need for high-quality guidelines for the design, conduct and reporting of pediatric clinical trials. It demonstrates that although guidelines on certain domains of pediatric clinical research exist, few are empirically based. Complementary to the already published methodological and regulatory guidelines, multiple empirically-based guidelines should be developed by content experts on the various different domains that are of importance in pediatric clinical research. The development of these guidelines should follow robust and transparent methodology, enhancing the likelihood of subsequent adoption by the scientific and regulatory authorities.

In the process of this review we created a checklist of items, classified by domain, that should be addressed in these future guidelines. We have also developed a comprehensive list of all possible items to be considered. We invite all stakeholders to come up with additional items that they think are required.
We believe that priorization of guideline development on specific issues has to be based on stakeholder input.

Registration of all pediatric clinical trials should be an important requirement, in order to prevent needless repetition of trials. One of the ultimate goals of good pediatric research is the development of a worldwide pediatric formularium that is evidence based. WHO has made the first step by developing the List of Essential Medicines for Children, and making

an appeal to governments, industries and all scientific organizations to recognize the need for the improvement of good quality pediatric research.

To attain this good quality research we feel that sufficient funding is needed for the development of high-quality guidelines for the design, conduct and reporting of this research. Resources are also needed for regularly updating these guidelines, for the optimal dissemination of these guidelines, and for implementation strategies for widespread adoption by journals, scientific organizations and regulators all throughout the world.

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Appendices

Appendix 1. Ethical guidelines

Year	Region	Guideline
1947	United States (US)	Nüremberg Code[12]
1979	US	Belmont report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research[10]
1983	US	45 Code of Federal Regulations (CFR) 46 Subpart D regulations: Additional Protections for Children Involved as Subjects In Research[13]
1995	US	Committee on Drugs, American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations[14]
1996	World	International Conference on Harmonization (ICH) Good Clinical Practice: consolidated guideline E6[15]
2000	World	World Medical Association. Declaration of Helsinki[11]
2000	United Kingdom (UK)	Royal College of Paediatrics and Child Health (RCPCH): Ethics Advisory Committee. Guidelines for the ethical conduct of medical research involving children[16]
2001	Europe	Directive 2001/20/EC[17]
2002	World	Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects[18]
2004	UK	Medical Research Council (MRC) Ethics Guide: Medical research involving children[19]
2003	Europe	Confederation of European Specialists in Paediatrics (CESP). Guidelines for informed consent in biomedical research involving paediatric populations as research participants[40]
2004	Europe	CESP. Ethical principles and operational guidelines for good clinical practice in paediatric research[20]
2006	Europe	Regulation (EC) No 1901/2006 and 1902/2006 of the European Parliament[21;30]
2008	Australasia	The Royal Australasian College of Physicians' (RACP) Paediatric Policy on Ethics of Research in Children[22]
2008	Europe	Ethical considerations for clinical trials on medicinal products conducted with the paediatric population[23]

Appendix 2: Laws and regulations in pediatric drug development

United States:	
1977	American Academy of Pediatrics Committee on Drugs – Report on study of drugs in children[64]
1979	Food and Drug Administration (FDA) articulates how to provide information on labelling
1983	45 Code of Federal Regulations (CFR) 46 Subpart D regulations: Additional Protections for Children Involved as Subjects In Research
1997	FDA Modernization Act/Exclusivity Provision[73]
1998	Pediatric Rule Regulation (enjoined 2002)[25]
2000	Guidance for Industry: International Conference on Harmonization (ICH) E11 Clinical Investigation of Medicinal Products in the Pediatric Population[66]
2001	Subpart D regulations adopted by FDA: Additional safeguards for children in clinical investigation of FDA-regulated products[13]
2002	Best Pharmaceuticals for Children Act (BPCA)[27]
2003	Pediatric Research Equity Act (PREA)[28]
2007	BPCA and PREA re-authorized by Congress[29]
Europe:	
2000	Regulation No (EC) 141/2000 on orphan medicinal products[74]
2000	ICH E11 Note for guidance on clinical investigation of medicinal products in the paediatric population[64;65]
2001	Directive 2001/20/EC Good Clinical Practice in Clinical Trials[17]
2003	Commission Directive 2003/94/EC principles and guidelines of good manufacturing practice[75]
2005	Commission Directive 2005/28/EC principles and detailed guidelines for good clinical [76]
2007	Paediatric Regulation No 1901/2006 and 1902/2006[21;30]
Japan:	
2000	Notification No. 1334: Clinical studies on Drugs in Pediatric Populations (ICH E11)[67]

Appendix 3: Search strategies for bibliographic databases

Pubmed (hits: 3750)	infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn) **AND** guideline* OR checklist* OR recommendation* OR standard* OR requirement* OR instruction* OR guidance* OR policies OR policy OR "Guideline"[Publication Type] **AND** "Clinical Trials as Topic"[Mesh] **Limit**: recent 10 years
Embase (additional hits: 29)	infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/ or adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/ or primary school/ or high school/ or kindergarten/ or nursery school/ or school/ or (infant$ or (newborn$ or new born$) or (baby or baby$ or babies) or neonate$).mp. or (child$ or (school child$ or schoolchild$) or (school age$ or schoolage$) or (pre school$ or preschool$)).mp. or (kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$).mp. or (minors$ or (under ag$ or underage$) or juvenil$ or youth$).mp. or (puber$ or pubescen$ or prepubescen$ or prepubert$).mp. or (pediatric$ or paediatric$ or peadiatric$).mp. or (school or schools or (high school$ or highschool$) or primary school$ or nursery school$ or elementary school or secondary school$ or kindergar$).mp. **AND** guideline$.mp. OR standard$.mp. or exp Standard/ OR checklist$.mp. or exp Checklist/ OR recommendation$.mp. OR requirement$.mp. OR instruction$.mp. OR guidance$.mp. OR exp Policy/ or policies$.mp. OR policy.mp. **AND** *clinical trial/ or *phase 1 clinical trial/ or *phase 2 clinical trial/ or *phase 3 clinical trial/ or *phase 4 clinical trial/ or *controlled clinical trial/ **AND** **Limit**: recent 10 years

Appendix 4: Searched websites

Organization	Country	Address
Pediatric Networks:		
American Academy of Pediatrics (AAP)	US	www.aap.org
Academic Pediatric Association (APA)	US	www.ambpeds.org
Asian Pacific Pediatric Association (APPA)	Australasia	www.appassoc.org
Canadian Paediatric Society (CPS)	Canada	www.cps.ca
European Academy of Paediatrics (EAP, formerly known as C.E.S.P.)	Europe	www.eapaediatrics.eu
Union of National European Paediatric Societies and Associations (EPA/UNEPSA)	Europe	www.epa-unepsa.org/
International Pediatric Association (IPA)	Worldwide	www.ipa-world.org
Medicines for Children Research Network (MCRN) NL	Netherlands	www.mcrn.nl
Medicines for Children Research Network (MCRN) UK	UK	www.mcrn.org.uk/
National Children's Bureau (NCB)	UK	www.ncb.org.uk
Pädiatrisches Netzwerk	Germany	www.paed-net.org
Royal Australasian College of Physicians (RACP)	Australia	www.racp.edu.au/
Royal College of Paediatrics and Child Health (RCPCH)	UK	www.rcpch.ac.uk
Task-force in Europe for Drug development for the Young (TEDDY)	Europe	www.teddynoe.org/
Regulatory authorities:		
Food and Drug Administration (FDA)	US	www.fda.gov
Australian Government, Department of Health and Ageing, Therapeutic Goods Administration	Australia	www.tga.gov.au
Directorate General (DG) Research	Europe	www.ec.europa.eu/research
European Union (EU) Law	Europe	www.eur-lex.europa.eu
European Medicines Agency (EMEA)	Europe	www.emea.europa.eu
European Union (EU)	Europe	www.ec.europa.eu
Medicines and Healthcare products Regulatory Agency (MHRA)	UK	www.mhra.gov.uk
Japanese Government, Ministry of Health, Labour and Welfare	Japan	www.mhlw.go.jp/english
National Health and Medical Research Council (NHMRC)	Australia	www.nhmrc.gov.au/
Pharmaceutical and Medical Safety Bureau Japan (PMSB)	Japan	www.pmda.go.jp/english
Other:		
Alberta Research Centre for Child Health Evidence (ARCHE)	Canada	www.ualberta.ca/ARCHE
Council for international organizations of medical sciences (CIOMS)	Worldwide	www.cioms.ch
Drug Information Association (DIA)	Worldwide	www.diahome.org
European Forum for Good Clinical Practice (EFGCP)	Europe	www.efgcp.be
General Medical Council (GMC)	UK	www.gmc-uk.org
International Conference on Harmonisation (ICH)	Worldwide	www.ich.org
International Pharmaceutical Federation (FIP)	Worldwide	www.fip.nl
Medical Research Council (MRC)	UK	www.mrc.ac.uk
Medicines and Healthcare products Regulatory Agency (MHRA former MCA)	UK	www.mhra.gov.uk
National Institute Health Research (NIHR)	UK	www.nihr.ac.uk
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	US	www.nichd.nih.gov
US National Institutes of Health (NIH)	US	www.nih.gov
World Health Organization (WHO)	Worldwide	www.who.int
World Medical Association (WMA)	Worldwide	www.wma.net

Appendix 5: Adapted AGREE instrument

Domain, Item nr	Item
Scope and purpose:	
1.	The objectives are specifically described (A1).
2.	The patients to whom the guideline is meant to apply are specifically described (A3).
Stakeholder involvement:	
3.	Target users of the guideline described (A6):
Rigour of development:	
4.	Systematic methods were used to search for evidence (A8).
5.	The criteria for selecting the evidence are clearly described (A9).
6.	The methods used for formulating the recommendations are clearly described (A10)
7.	There is an explicit link between the recommendations and the supporting evidence (A12).
8.	Was the guideline developed using a consensus method?
9.	The guideline has been externally reviewed by experts prior to its publication (A13).
10.	A procedure for updating the guideline is provided (A14).
Clarity and presentation:	
11.	Key recommendations are easily identifiable (A17).
12.	The guideline is supported with tools for application (A18).
Applicability:	
13.	The potential organizational barriers in applying the recommendations have been discussed (A19).
Editorial independency:	
14.	Conflict of interest are described (A23).

A1 means that item 1 of the original AGREE form is used.

Appendix 6: Scientific publications containing recommendations

Author	Year	Country of authors	Patient group	Scope
General Medical Council[35]	2001	United Kingdom (UK)	All humans	Clinical trials: general research standards
Greenhill[36]	2003	United States (US)	Preschool children requiring psychopharmaca	Clinical trials: ethical, practical, scientific and regulatory recommendations
Kaufmann[37]	2000	US	All children	Clinical trials: problems and pitfalls
Schreiner[38]	2003	US	All children	Clinical trials: review on pediatric drug development
Derivan[39]	2004	US	All children	Ethics: role of placebo use
Gill[40]	2003	Europe	All children	Ethics: informed consent
Gill[20]	2004	Europe	All children	Ethics: good clinical practice
Hoop[41]	2008	US	Children with psychiatric disorder	Ethics: all issues
Kopelman[42]	2004	US	All children	Ethics: risk
McIntosh[16]	2000	UK	All children	Ethics: all aspects
Rosato[43]	2000	US	All children	Ethics: child's view
Sheikh[44]	2008	Ireland	All children	Ethics: medico-legal issues of clinical trials in Ireland
Ungar[45]	2006	US	All children	Ethics: documentation of assent
Anand[46]	2005	US, Canada	Neonates	Ethics and design: in clinical trials on analgesia and anesthesia
Twycross[47]	2008	UK	Young children	Ethics and design: assent process
Knox[48]	2007	US	All children	Ethics and design: ethical and legal issues of participation
Cramer[49]	2005	Canada, Australia US, South Africa	All children	Design: methodological issues
Pasquali[50]	2002	US	Children with hypertension	Design: trial design and analysis

Appendix 7a: Overview of included guidelines internet search

	Year	Title guideline	Author(s)	Region
1	2002	International ethical guidelines for biomedical research involving human subjects[18]	CIOMS	Worldwi
2	2007	National Statement on Ethical Conduct in Research Involving Humans[51]	ANHMRC	Australia
3	1998	NIH policy guidelines on the inclusion of children as participants in research involving human subjects[26]	NIH	US
4	2001	Perspectives on medical research conducted in children[52]	National advisory board	Finland
5	2000	FIP statement of principle: Pharmaceutical research in paediatric patients[53]	FIP	Worldwi
6	2003	Health Canada Addendum to ICH guidance document E11: Clinical investigation of medicinal products in the pediatric population[54]	Ministry of Health	Canada
7	2008	The Royal Australasian College of Physicians' Paediatric policy on ethics of research in children'[22]	RACP	Australia
8	2004	Medical Research Council (MRC) Ethics Guide: Medical research involving children[19]	MRC	UK
9	2007	Recommendations on ethical issues on medicine for children for European and National Institutions preparation (including issues on clinical trials) D079[55]	TEDDY	Europe
10	2000	Clinical investigation of medicinal products in the pediatric population E11[5]	ICH	Worldwi
11	2001	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[17]	EC	Europe
12	2008	Ethical considerations for clinical trials on medicinal products conducted with the paediatric population[23]	EC	Europe
13	2009	Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006[56]	EC	Europe
14	2007	Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population[57]	EMEA	Europe
15	2007	Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population[58]	EMEA	Europe
16	2006	Guideline on Clinical Trials in small populations[59]	EMEA	Europe
17	2003	Addendum on Paediatric Oncology to the Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3)[60]	EMEA	Europe
18	2007	Guideline on the investigation of medicinal products in the term and preterm neonate[61]	EMEA	Europe
19	2005	Reflection paper on formulations of choice in paediatric population[62]	EMEA	Europe
20	1998	General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products[63]	FDA	US
21	2001	Additional safeguards for children in clinical investigation of FDA-regulated products[13]	FDA	US
22	2004	Textbook of clinical trials, chapter: clinical trials in pediatrics[8]	Karlberg	UK

Appendix 7b: Overview of excluded guidelines internet search

Year	Title guideline	Authors	Region
2008	Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects	WMA	Worldwide
1997	Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: European Treaty Series – No 164	CHRB	Worldwide
2005	Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research	CHRB	Worldwide
2001	Guidelines on ethics of medical research: general principles	MRC SA	SA
2004	The United Kingdom (UK) Medicines for Human Use (Clinical Trials) Regulations	UK	UK
2002	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans	TC	Canada
2005	Universal Declaration on Bioethics and Human Rights	UNESCO	Worldwide
2006	Standards for the development of clinical guidelines and implementation in paediatrics and child health	RCPCH	UK
1989	United Nations (UN) Convention on the Rights of the Child (20/11/1989)	UN	Worldwide
2008	FIP statement of policy: Quality Use of Medicines for Children	FIP	Worldwide
1997	draft Guidelines on the "Inclusion of Pediatric Subjects in Clinical Trials" (withdrawn after ICH E11)	Health Canada	Canada
2007	Guidance Notes for Involving Children and Young People in Research	MCRN	UK
2003	Guidelines for Research[79]	NCB	UK
unpubl.	Guidance document on the clinical considerations for the assessment of pharmacokinetics and PD/PK bridging studies in children	TEDDY	Europe
unpubl.	Document on definition of PD/PK principles for evaluating exposure effect relationship in children	TEDDY	Europe
unpubl.	Guidance document on methodological aspects for clinical trial in children	TEDDY	Europe
2007	Guidance on clinical trials conduct for parent, children and general public D060	TEDDY	Europe
2007	Recommendations on pharmacovigilance D077	TEDDY	Europe
2004	A guide to Actively Involving Young People in Research	INVOLVE	UK
1996	Good Clinical Practice: consolidated guideline E6[15]	ICH	Worldwide
1998	General Consideration of Clinical Trials E8	ICH	Worldwide
1998	Statistical principles for clinical trials E9	ICH	Worldwide
2000	Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals	ICH	Worldwide
2008	Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies	EC	Europe
2009	List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006 and its implementing guideline 2009/C28/01	EC	Europe
2008	Concept paper on the development of a quality guideline on pharmaceutical development of medicines for paediatric use	EMEA	Europe
2008	Guideline on the need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications	EMEA	Europe
2003	Discussion paper on the impact of renal immaturity	EMEA	Europe
2005	Concept paper on the impact of liver immaturity	EMEA	Europe
2006	Concept paper on the impact of lung and heart immaturity	EMEA	Europe
2006	Concept paper on the impact of brain immaturity	EMEA	Europe
2006	Nonclinical Safety Evaluation of Pediatric Drug Products	FDA	US
2005	How to Comply with the Pediatric Research Equity Act (draft guidance)[80]	FDA	US
1999	Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act	FDA	US
2000	Pediatric Oncology Studies In Response to a Written Request (draft guidance)	FDA	US
1996	Content and Format of Pediatric Use Supplements	FDA	US
2007	Information in English on Japan Regulatory Affairs.[32]	JPMA	Japan
2007	Textbook: Guide to Paediatric Clinical Research[81]	Rose	Suisse

Abbreviations: CHRB, Convention on Human Rights and Biomedicine; EC, European Commission; EMEA, European Medicines Agency; FDA, Food and Drug Administration; FIP, International Pharmaceutical Federation; HCTPD, Health Canada Therapeutic Products Directorate; ICH, International Conference on Harmonization; JPMA, Japan Pharmaceutical Manufacturers Association; MCRN, Medicines for Children Research Network; MRC, Medical Research Council; NCB, National Children's Bureau; RCPCH, Royal College of Paediatrics and Child Health; SA, South Africa; TC, Tri-Councils; unpubl, unpublished; TEDDY, Task-force in Europe for Drug Development for the YounUN, United Nations; US, United States of America; UNESCO, United Nations Educational, Scientific and Cultural Organization; WMA, World Medical Association

Appendix 8a: Description of internet guidelines

Nr	1[18]	2[51]	3[26]	4[52]	5[53]	6[54]	7[22]
Document	CIOMS guidelines	ANHMRC guidelines	NIH Policy	Finnish ethical recommendations	FIP statement of principle	Health Canada addendum	RACP ethical policy
Year of development	2002	2007	1998	2001	2000	2003	2008
Scope	Effective application of ethical guidelines for biomedical research, particularly in developing countries	Ethical of pediatric research, clarifying responsibilities of institutions, investigators and reviewers	Increasing participation of children in clinical trials	Ethical questions concerning medical research in children	Pharmaceutical research in children	Regulatory considerations for the timing and conduct of clinical trials in children	Application of RACPs principles of ethical research in children
Patient group	Humans, including children	Humans, including children	Children <21 y	Children <18 y	Children	Children	Children <18 y
Country	Worldwide	Australia	United States	Finland	Unknown	Canada	Australasia
Development group	CIOMS	ANHMRC	NIH	National Advisory Board	FIP	Health Canada	RACP
Type develop. group	Non-governmental, non-profit	Government	Government	Government	Pharmaceutical industry	Government	International pediatric network
Composition develop. group	Not described	Not described	Not described	Parent, nurse, pedatrician, nat. advisory board, pharmacologist, law representative	Industry	Government	Pediatrician, others
Target users	Policy-makers, reviewers of research, investigators	Investigators, participants, industry, IRB, research governance, public	Investigators, IRB, peer review groups, advisory councils	Not described	Not described	Investigators, Industry	Pediatricians, Investigators, the public

Abbreviations: ANHMRC, Australian National Health and Medical Research Council; CIOMS, Council for International Organizations of Medical Sciences; IRB, Institutional Review Board; NIH, National Institutes of Health; RACP, Royal Australasion College of Physicians

Appendix 8a-continued

Nr	8[19]	9[55]	10[5]	11[17]	12[23]	13[56]	14[57]
Document	MRC ethics guideline	TEDDY Ethical recommendations	ICH E11 guideline	EU Clinical trial directive	EU ethical guideline	EU Eudra-CT pediatric guideline	EMEA pharmacokinetics guideline
Year of development	2004	2007	2000	2001	2008	2009	2006
Scope	Support for MRC proposals concerning the ethical conduct of pediatric research	Recommendations for regulatory agencies on ethical issues of pediatric research	Critical issues in clinical drug trials in children	Good clinical practice and ethics of clinical trials	Ethics in pediatric research (promotion and protection of the dignity, the well-being and the rights of children)	Registrations pediatric clinical trials	Recommendations on pharmacokinetic aspects of pediatric drug research
Patient group	Children <18 y	Children	Children	Humans, including children	Children <18 y	Children	Children <18 y
Country	United Kingdom	Europe	Worldwide	Europe	Europe	Europe	Europe
Development group	Medical Research Council (MRC)	TEDDY	ICH	European Parliament and Committee	Ad hoc group for developing guidelines for Directive 2001/20/EC	European Committee (EC)	EMEA, Committee for Medicinal Products for Human use (CHMP)
Type develop. group	National scientific organization	Pediatric network of excellence	International scientific organization	Government	Government	Government	Regulator
Composition develop. group	Not described	Not described	Expert working group	Not described	Not described	Not described	Regulator
Target users	Researchers, clinicians, reviewers of research, public, IRB	Public, regulators, EC, TEDDY	Regulators	Not described	Sponsors, regulators, investigators, IRB, industry, pediatricians insurance companies, applicants, patients,	Not described	Applicants

ICH, International Conference on Harmonization; IRB, Institutional Review Board; TEDDY, Task-force in Europe for Drug Development for the Young

Appendix 8a-continued

Nr	15[58]	16[59]	17[60]	18[61]	19[62]	20[63]	21[13]	22[8]
Document	EMEA pharmacovigilance guideline	EMEA small population guideline	EMEA pediatric oncology addendum	EMEA neonatal guideline	EMEA paper on pediatric formulations	FDA considerations pharmacokinetics in children	FDA regulation for pediatric research	Textbook Pediatric clinical trials
Year of development	2007	2006	2003	2007	2006	1998	2001	2004
Scope	Pharmacovigilance in pediatric trials	Methods for design and analysis of clinical trials in small populations	Specific regulatory requirements related to trials in pediatric oncology	To provide guidance for the development of medicinal products for use in the neonatal population	Guidance for development and manufacture of pediatric formulations	General considerations for conducting pharmacokinetic studies in pediatric populations	Safeguards for clinical research in children	Critical issues in clinical drug trials in children
Patient group	Children <18 y	Small populations, e.g. children	Children with cancer	Neonates (0-1 month)	Children	Children <16 y	Children	Children
Country	Europe	Europe	Europe	Europe	Europe	United States	US	Hong Kong
Development group	EMEA, Committee for Medicinal Products for Human use (CHMP), pharmacovigilance Working Party	EMEA, CHMP	EMEA, Committee for Proprietary Medicinal Products (CPMP)	EMEA, CHMP, paediatric working party	EMEA, CHMP, paediatric working party, quality working party	Food and Drug Administration (FDA), Center for Drug Evaluation and Research	FDA	Karlberg
Type develop. group	Regulator	Regulator	Regulator	Regulator	Regulator	Regulator	Regulator	Single person
Composition develop. group	Regulator	Regulator	Regulator	Regulator	Regulator	Regulator	Regulator/ government	Scientist
Target users	All those involved in the conduct of pediatric clinical trials	Not described	Not described	Applicants, sponsors	Not described	Applicants	Not described	Not described

EMEA, European Medicines Agency;

Appendix 8b: Checklist of contents of internet guidelines

Domain, item	Guideline number																				
	1[18]	2[51]	3[26]	4[52]	5[53]	6[54]	7[22]	8[19]	9[55]	10[5]	11[17]	12[23]	13[56]	14[57]	15[58]	16[59]	17[60]	18[61]	19[62]	20[63]	21[13]	22
Ethics																						
Risk/benefit assessment	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	-	+	+	+	-	+	+
Minimizing burden	+	+	-	+	-	-	+	+	+	+	+	+	-	-	-	-	-	+	-	-	+	+
Use of placebo/comparators	+	-	-	+	-	-	-	-	+	-	-	+	-	-	-	+	-	+	-	-	-	+
Age of consent/assent	-	+	+	+	+	-	+	+	+	+	-	+	-	-	-	-	-	-	-	-	-	+
Informed consent procedure	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	+	+	+	+
Reimbursement/reward	+	+	-	-	+	-	+	+	-	+	+	+	-	-	-	-	-	-	-	-	-	+
Use of healthy subjects	+	-	-	+	-	+	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	+
Role of ethics board	+	+	+	-	+	-	+	+	+	+	+	+	-	-	-	-	-	+	-	+	+	+
Design																						
Timing of study	-	-	-	-	+	+	-	-	-	+	-	+	-	-	+	-	+	+	-	-	-	+
Study designs	-	-	-	-	-	-	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
Methods of recruitment	-	-	-	-	+	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	+
Age classifications	-	-	+	+	+	-	-	-	-	+	-	+	-	+	+	-	-	+	+	+	-	+
Age subgroup analysis	-	-	-	-	+	-	-	-	-	+	-	-	-	+	+	-	+	+	-	-	-	+
Other stratification criteria	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	+	-	+	-	+	-	-
Multi-center studies	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility criteria	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	+
Sample size problems	-	-	-	-	-	-	-	+	-	+	-	+	-	-	+	+	-	+	-	+	-	+
Information use from other studies	-	-	-	-	+	+	-	+	-	+	-	+	-	+	+	+	+	+	+	+	-	+
Post-marketing surveillance	-	-	-	-	-	+	-	-	-	+	-	-	-	-	+	-	+	+	-	-	-	+
Practical issues																						
Economic barriers	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Logistical/infrastructural barriers	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	+
Technical issues	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-

Appendix 8b-continued

	Guideline number																					
Domain, tem	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Procedures																						
Blood sampling	-	-	-	+	-	-	-	+	-	+	-	+	-	+	-	-	-	+	-	+	-	+
Other interventions	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	+	-	-
Pharmacology																						
Dosing	-	-	-	+	+	-	-	-	-	+	-	-	-	+	+	-	+	+	+	+	-	-
PK/PD	-	-	-	-	+	-	-	-	-	+	-	-	-	+	+	-	+	+	-	+	-	+
Formulation, including different concentrations	-	-	-	-	-	-	-	-	+	+	-	+	-	+	+	-	-	+	+	-	-	+
Route of administration	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-
Excipients	-	-	-	-	-	-	-	-	-	+	-	+	-	-	+	-	-	+	+	-	-	-
Adherence	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-
Weight or body surface adjustments	-	-	-	+	-	-	-	-	-	+	-	-	-	+	-	-	+	+	+	+	-	-
Role of growth, maturation, development	-	-	-	-	-	+	-	-	-	+	-	-	-	+	+	-	-	+	+	+	-	+
Outcomes																						
Child-specific outcomes	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	+	-	-	-	+
Age- en development specific outcomes	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+
Measurement instruments	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+
Safety/toxicity/adverse events	-	+	-	-	+	-	+	+	+	+	+	+	-	+	+	-	+	+	-	+	-	+
Long-term safety	-	-	-	+	+	-	-	+	+	+	-	+	-	-	+	+	+	+	-	-	-	+
Effect of drug on growth, maturation, development	-	-	-	+	+	-	-	-	-	+	-	+	-	-	+	-	+	+	-	-	-	+
Statistics																						
Statistical methods	-	-	-	-	-	-	-	-	-	+	-	+	-	+	+	+	-	+	-	+	-	+
Population pharmacokinetics	-	-	-	-	-	-	-	-	-	+	-	+	-	+	-	-	-	+	-	+	-	-
Reporting																						
Requirement of publication	-	-	-	-	-	-	+	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-
Time frame of publication	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
Reporting results to participants	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Appendix 8c: Quality appraisal of internet guidelines

	Guideline																					
Appraisal for:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Scope and purpose (0-2)	0	1	2	1	0	1	0	0	1	1	0	1	1	1	2	0	2	2	2	1	1	1
Stakeholder involvement (0-1)	0	1	1	0	0	1	1	1	1	0	0	1	1	1	1	0	0	1	0	1	0	0
Rigour of development (0-7)	1	3	0	1	0	0	0	1	2	1	0	0	0	0	0	0	0	0	0	0	3	1
Clarity and presentation (0-2)	1	1	0	1	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1
Applicability (0-1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Editorial independence (0-1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 1. Selection process of the bibliographic databases literature search