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Children's presence in research. A review of online registers

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Abstract

Objectives To determine how many online clinical trial registers include paediatric trial data, how much information is provided, ease of searching for paediatric trials and the accessibility of paediatric trial data in general.

Methods Medline and Google were searched for mention of clinical trial registers in July 2008. All registers considered to be eligible were evaluated for trial information provided, search options available, and number of trials, both total and paediatric. A meta-analytic weighted average of the presence of paediatric trials was calculated and compared to the percentage of published paediatric trial articles in Medline. The paediatric trials in the registers were searched for in the World Health Organization's International Clinical Trials Registry Platform (ICTRP). All online, freely accessible registers including ongoing trials on different drugs or therapeutic areas, were eligible for review.

Results Twelve registers were included in the review. All except one provided detailed trial data, while search options varied between registers: seven provided free-text searching, two listed their trials by condition, two provided elaborate search options (age group, condition, study purpose, etc) and one simply listed its trials. Nine of the 12 registers' search facilities made it possible to search for paediatric trials, and these were analysed further: the percentage of paediatric trials in the single registers ranged from 4.8 to 33.3%, and the weighted average was 15% (95% confidence interval 8.2–21.8). The percentage of

published, paediatric trial articles was 25%. Of the paediatric trials also searched for in the ICTRP, 66% were found.

Conclusions Great difficulty was found in retrieving paediatric trials due to the limited and inadequate search functions of the registers reviewed but, in general, the registers seem to represent fewer paediatric trials than those reported in the literature. The ICTRP portal is important for trial accessibility, but it is still in an initial phase and far from representative of the global research situation, especially in the field of paediatrics.

Keywords Clinical trials as topic · Internet · Pediatrics · Registries · Review

Abbreviations

EMA European Medicines Agency
ICMJE International Committee of Medical Journal Editors
ICTRP International Clinical Trials Registry Platform
MeSH Medical Subject Headings

What this paper adds

What is already known on this subject

Registers are an important source of information for healthcare professionals, funding agencies and for anyone interested in participating in a trial. They have an important role in preventing trial duplication and, therefore, in avoiding any potential waste of effort and resources as well as in dealing with publication bias and, therefore, overcoming distorted evidence.

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Paediatric studies are more problematic than those in adults so fewer studies are carried out in this population, leading to insufficient knowledge on drug therapies. This fact makes access to the limited amount of data from paediatric trials even more important.

Legislative efforts aimed at encouraging paediatric trials and at registering trials in online registers to make the data more accessible have intensified in the last decade.

What this study adds

- It is difficult to identify paediatric trials in many online registers due to the limited and inadequate search functions of many of the registers. In addition, the number of paediatric trials compiled in these registers seems to be lower than that present in the published literature [meta-analytic weighted average of 15.0% with 95% confidence interval (CI) 8.2–21.8, compared to 25%].
- The World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP) portal represents an important tool in terms of trial accessibility. Although it is still in an initial phase and far from representative of the global research situation, especially in the paediatric field, it is likely that in the future this initiative will have an important role in assisting and promoting paediatric clinical research.

Introduction

Trial registers are computerized databases that collect information on studies. The scope of the trials can be limited to, for example, a specific disease, population or geographical location. Registers are an important source of information not only for healthcare professionals but also for funding agencies when decisions have to be made regarding funding allocations as well as anyone interested in participating in a trial. Registers have an important role in preventing trial duplication (as opposed to replication) and, therefore, in avoiding any potential waste of resources and effort [1, 2], but they are also invaluable to researchers conducting systematic reviews and to professionals compiling guidelines, since they are the only means of tracking research results, whether published or not [3, 4]. Research that has negative or inconclusive results, in fact, often does not get published, despite the ethical imperative to provide a public record of such research [5, 6]. When only positive studies, or only a study's positive outcomes, are published [7], the result is publication bias, and this can lead to distorted evidence in the literature [8–10].

As a result of the increased attention paid to the need for data accessibility in the last few years [11], especially after a much publicized scandal in which a pharmaceutical company withheld data that showed increased suicidal tendencies with the use of antidepressants in children [12], many registers have been created, also by drug companies. Concurrently, even greater pressure has been placed on researchers, through different initiatives, to register their trials [13, 14]. The methods for registering data have been gradually defined in more detail and involve public registers that fit certain criteria. These initiatives have helped increase the number of trials registered and seem to be generally well-accepted by researchers [15].

Paediatric studies are more problematic than those in adults [16, 17], have higher research costs and lead to results that are in the interest of a population with a smaller market size [18]. Fewer studies are therefore carried out in this population, leading to insufficient knowledge on drug therapies and significant off-label drug use. In addition, online registers often do not provide adequate search functions for finding paediatric studies, making it even more difficult to find data on the already scarce number of trials in children.

Legislative efforts aimed at encouraging paediatric trials, the most recent of which is the Paediatric Regulation in Europe [19], have intensified in the last decade and will lead to an increase in such studies, to an improvement in their design and strength [20], to more focus on priority disease areas [21] and, hopefully, also to higher publication rates [22].

We have reviewed freely accessible, online registers to determine how many of these include paediatric clinical trial data, how much information is provided and the ease of searching for paediatric studies.

Methods

Search for clinical trial registers

The Medline database and Google were searched for any mention of clinical trial registers in July 2008. Most of the terms used for the Medline search were chosen from among the National Library of Medicine's Medical Subject Headings (MeSH) and included: "registries", "clinical trials as topic", "internet" and "databases as topic". The search combination used was "Internet"[Mesh] AND ("Registries"[Mesh] OR register OR registry) AND ("Clinical Trials as Topic"[Mesh] OR "Databases as Topic"[Mesh]). The terms used for the Google search also included synonyms, since there is no defined term dictionary to use for general search engines. The additional terms

used, alone or in combination with each other, were “health research register” and “trial register”. The websites of the registers found were searched for links to additional registers.

Register criteria

In order to be considered in the review, the resulting registers had to be freely accessible, had to involve multiple drugs or therapeutic areas and had to include data on ongoing clinical trials, as opposed to only data on trial results. The registers of small pharmaceutical companies (e.g. Antigenics and Chiron) were excluded because they only included a few trials on their products.

A first screening was performed to eliminate websites that only listed a few trials, such as some medical clinic websites or small research centres.

Register evaluation

Once the final set of registers was selected, each register was evaluated for trial information provided, search options available, total number of trials included and number of paediatric trials. The latter parameter was estimated by using the search options available, with every effort made to arrive at the most precise number of paediatric trials. When only free-text searching of trial records was available, searching involved various terms related to paediatrics. In some cases, the search options were limited, and in order to arrive at a final, estimated number of paediatric trials, we first had to search for single terms individually and then compile the resulting sets of trials in Microsoft Excel to eliminate all duplicates.

Meta-analytic weighted average

A meta-analytic weighted average and 95% CIs of the presence of paediatric trials in the registers were calculated.

Search for published trial articles

A search of the Medline database for articles published in the 2005–2007 period reporting the results of clinical trials or intervention studies was also performed to determine whether the percentage of paediatric trials present in the registers was representative of the actual number of paediatric studies carried out. To do this, the number of articles found involving infants, children or adolescents was compared to the total number of articles from the same period. In order to avoid bias in analysing the literature from only the 2005–2007 period, we repeated the search for two additional 3-year periods (1985–1987 and 1995–1987).

Search for paediatric trials in the WHO’s ICTRP

Paediatric trials found in the registers were also searched for in ICTRP to assess their presence and thus evaluate their accessibility at an international level.

Results

Using the criteria described, we originally found 108 online registers. Of these, 88 were excluded, mostly because they concerned a specific therapeutic area (especially cancer). However, some were excluded because they were not searchable registers, but only allowed users to insert personal health information to then be informed of any trials in which they were eligible to participate, and others because they only included trial results. The Current Controlled Trials’ meta-Register was also excluded because it was considered to be not a register, but a system designed to search multiple registers at once.

The review initially included a total of 19 online registers. From this set, however, two were excluded because they only covered trials run in their own centres (Mayo Clinic and St. Jude Children’s Hospital), two because they no longer provided trial information, but linked to Clinicaltrials.gov (Clinicaltrials.gov) for trial details (Abbott, Lilly) and three because they stopped, not been updated or were inaccessible (National Research Register, DEC-net, and DrugsOnTrial, respectively). The resulting 12 registers were reviewed and their characteristics described. (see Table 1)

Description of the 12 registers

Of the 12 registers considered, two were pharmaceutical company registers, one was the Association of the British Pharmaceutical Industries’ (ABPI) register and nine were public service registers run by governments, ministries of health and/or hospitals or funded by the European Union. One register, the National Organization for Rare Disorders Register (NORD) was significantly different from the rest, both in size and in type of trials covered.

None of the registers required registration. The number of trials included in the various registers ranged from 15 (NORD register) to 58,261 trials (Clinicaltrials.gov).

All of the registers provided detailed trial data (from among information such as title, drug studied, disease, objective, phase, design, duration, study status, eligibility criteria, contact information, participating centres and resulting publications), except for the NORD register, which only provided a brief description of the trials, but specified an email or website related to each trial for additional information. All of the data fields of the registers

Table 1 General characteristics of trial registers

Number of trial	Name of register	URL	Register run by	Types of trials included in register	Accessibility of information
1	AMGEN	http://www.amgentrials.com/	Human therapeutics company in the biotechnology industry	Phase 2, 3 and 4 safety or efficacy clinical trials of Amgen products.	Provides data to Clinicaltrials.gov
2	Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/	Group supported by the National Health and Medical Research Council	All clinical trials involving Australian/New Zealand researchers or participants.	Is a Data Provider ^a of WHO ICTRP
3	Chinese Clinical Trial Register	http://www.chictr.org/Site/Search.aspx?lang=EN	Non-profit organization	Intervention trials (drug or non-drug treatments), observational studies, case-control or cohort studies, prevention and prognosis studies, etc.	Is a Primary Registry ^b of WHO ICTRP
4	Clinicaltrials.gov	www.clinicaltrials.gov	Service of the U.S. National Institutes of Health	Federally and privately supported clinical trials conducted in the USA and around the world.	Is a Data Provider of WHO ICTRP
5	India–Clinical Trials Registry (CTRI)	http://www.ctri.in:8080/Clinicaltrials/trials_jsp/index.jsp	National public service.	Intervention trials (drug, surgical procedure, preventive measures, lifestyle modifications, devices, behavioural treatment, etc).	Is a Primary Registry of WHO ICTRP
6	International Standard Randomized Controlled Trial Number (ISRCTN) Registry	http://www.isrctn.org/	Non-profit organization	Any clinical trial designed to assess the efficacy of health interventions.	Is a Data Provider of WHO ICTRP
7	Medical Research Council (MRC)	http://www.ctu.mrc.ac.uk/Register.asp	Publicly funded centre for clinical research	Mostly RCTs comparing two or more treatments	Does not say. Contributes to meta-Register of controlled trials (http://www.controlled-trials.com/mrct)
8	The Netherlands Trial Register	http://www.trialregister.nl/	Group partially based on volunteers, part of Dutch Cochrane Centre	All studies designed to assess the impact/efficacy of healthcare interventions (drugs, surgical procedures, devices, behavioural therapies, etc).	Is a Primary Registry of WHO ICTRP
9	National Organization for Rare Disorders (NORD) Register	http://www.rarediseases.org/research/clinicaltrials	Non-profit, voluntary health agency	Any trials on rare diseases currently recruiting patients.	No mention of contribution of data to a WHO/ICMJE acknowledged registry
10	Roche	http://www. Roche-trials.com/registry.html	Healthcare company	Ongoing Phase I–IV clinical studies and interventional studies on advanced diagnostic products.	Contributes to Clinicaltrials.gov (and other “local” registers)
11	Sri Lanka Clinical Trials Registry	http://www.slctr.lk/	Not-for-profit registry	Trials on effects of healthcare interventions conducted in Sri Lanka or overseas. Includes also nutrition and other non-drug trials.	Is a Primary Registry of WHO ICTRP
12	UK pharmaceutical industry (ABPI)	https://www.cmrinteract.com/clintrial/	Association of the British Pharmaceutical Industry	Pharmaceutical Industry clinical trials initiated by the Association of the British Pharmaceutical Industry (ABPI) and sponsored by the industry.	No mention of contribution of data to a WHO/ICMJE acknowledged registry

WHO, World Health Organization; ICTRP, International Clinical Trials Registry Platform; RCT, random controlled trial

^a ICTRP Data Providers are registers linked to the WHO’s ICTRP platform, which can be searched contemporaneously. At the present time, these registers are the Australian New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov and ISRCTN.org

^b A Primary Registry meets specific criteria, among which is the collection of the 20 data items known as the WHO Trial Registration Data Set (<http://www.who.int/ictpr>), but whose trials cannot be search for through the portal

were essentially complete, with the exception of the ABPI register, whose data fields were often left blank and whose trial records were often outdated.

The search options provided by the different registers varied (See Table 2), but most (seven registers) provided free-text searching only. The Netherlands Trial Register's free-text searching, however, did not give the desired results, and searching was difficult since no English-language instructions were provided on its site. In addition, two of these seven registers only searched within the trial titles. Two registers grouped their trials into lists of conditions (one of which listed "paediatrics" as a condition) that users could select, two provided elaborate search options (by age group, condition, study purpose, sponsor type, etc) and one simply listed its trials.

Only these last two registers and the register providing a list of trials grouped under the "paediatric" condition facilitated searching for paediatric trials.

The two registers that only searched free-text within the title field and the register that simply listed the conditions under which the single trials were grouped were excluded from further analyses because the paediatric trials could only be searched for by opening each single trial record and attempting to find information on the population's age.

Paediatric trials

The nine registers for which it was possible to identify paediatric studies all included at least one paediatric trial, for a total of 17,200 trials involving children (see Table 2). The percentage of paediatric trials in these nine registers ranged from 4.8 to 33.3%. The meta-analytic weighted average, adjusted and weighted by sample size, was 15.0% (95% CI 8.2–21.8). The percentage of articles involving paediatric clinical trials compared to all clinical, based on a search of the Medline database, was estimated to be 25%.

The paediatric trials from the registers covered different therapeutic areas, from cancer to infectious diseases. Some of the registers, such as that of the government of India, also included trials on non-pharmacological interventions, such as the use of toothpaste. An evaluation of which therapeutic areas were most common among all registers was found to be too difficult because of the limited search options.

To assess the presence of the paediatric trials in the WHO's ICTRP, we selected the six registers that were not directly searchable through the ICTRP. All of the paediatric trials found in these six registers (210 trials) were then searched for their presence in the ICTRP, and the number of trials present was noted. Specifically, seven of the nine paediatric trials from the Amgen register were present in the ICTRP, zero of the eight trials from the Chinese register, six of the 25 trials from the Indian register, two of the 11 trials

from the MRC, 121 of the 152 trials from the Netherlands' register and three of the five trials from the NORD register. In all, therefore, 71 of the paediatric trials (34%) were not found in the ICTRP.

Discussion

Many clinical trial registers exist—in 2004, the estimate was over 300 [23]—and most are specific to disease areas or geographic locations. The effects of trial registration in one public register, once the database was acknowledged by the international movement, were documented in a 2005 study and resulted in a considerable increase in the number of trials registered as well as an improvement in data record completeness [24]. Initiatives such as the WHO and International Committee of Medical Journal Editors' (ICMJE) jointly acknowledged list of 20 data items [14] have helped standardize the type and format of data to be collected by registers. The adherence to and enforcement of these criteria have resulted in registers becoming more easily searchable and their data more complete and dependable.

Although national trial registers are important [25], it is essential that few, large, comprehensive registers represent the worldwide clinical trials situation, so that trial data can be accessed easily and quickly, without the interested party having to search too many sources and without the presence of too many duplicate entries. Large-scale initiatives with such a goal in mind are the meta-register of controlled trials (www.controlled-trials.com/mrct) and, more recently, the WHO's ICTRP platform [26], from which a few, selected registers can be searched contemporaneously. These registers, known as ICTRP Data Providers, are, currently, the Australian New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov, and ISRCTN.org. The WHO also provides a list of "Primary Registries" that meet specific criteria, among which is the collection of the 20 data items known as the WHO Trial Registration Data Set (<http://www.who.int/ictrp>), but whose trials cannot be searched for through the portal. There are several Primary Registries, and some were included in this review (See Table 1).

DEC-net was the only international register dedicated to the paediatric population [27, 28], and it was aimed at giving paediatric trials more visibility and facilitating the search for such trials on the part of the public and researchers. With the international initiatives aimed at increasing the importance of suitable registers and making paediatric data accessible, however, such a register is no longer necessary. The most essential factor is that data on paediatric trials be made easily available, and this can be done by providing adequate search options. The WHO is

Table 2 Details of trial registers

Trial number	Name	Search options provided	Number of paediatric trials	Number of trials in register	Percentage of paediatric trials	95% CI	Search strategy used to find paediatric trials
1	AMGEN	Trial listing by condition (includes "pediatric" condition)	13	269	4.8	1.2–5.5	All trials under "Pediatric" condition (no paediatric trials were found listed under other conditions).
2	Australian New Zealand Clinical Trials registry	Various	192	2264	8.5	7.3–9.6	Age range: <18 years
3	Chinese Clinical Trial Register	Free text search	8	94	8.5	2.8–14.2	Searched the following terms individually, then excluded duplicates: child, infant, paediatric, pediatric, adolescent, toddler, baby, babies, neonate, newborn.
4	Clinicaltrials.gov	Elaborate search options	15,190	58,261	26.1	25.7–26.4	Age range: <18 years
5	India - Clinical Trials Registry (CTRI)	Free text search (in any of a list of fields)	27	86	31.4	19.4–38.7	Searched the following terms individually, then excluded duplicates: paediatric, pediatric, child, children, kids, adolescent, infant, newborn, toddler, baby, babies, neonate.
6	ISRCTN	Free text search	1,608	6,939	23.2	22.2–24.2	Search string: "pediatr% OR paediatr% OR adolesc% OR neonat% OR newborn% OR infant OR child% OR toddler OR babies OR baby OR kids", where % is the symbol for word truncation.
7	MRC	Free text search	15	253 ^a	5.9	1.8–6.9	Searched the following terms individually, then excluded duplicates: paediatric, pediatric, child, children, kids, adolescent, infant, newborn, toddler, baby, babies, neonate.
8	The Netherlands Trial Register	Not clear. Has a search box, but does not perform normal free-text search; it may search through only key-words	152	1280	11.9	10.1–13.6	Searched the following terms individually, then excluded duplicates: child, infant, paediatr, pediatric, adolescent, toddler, baby, babies, neonate, newborn.
9	NORD	Trial listing; no search options	5	15	33.3	8.6–58.0	Checked records individually (three trials not specified, therefore not considered to be paediatric)
10	Roche	List by product name or by condition	-	400 ^a	-	-	Not possible to identify paediatric trials
11	Sri Lanka Clinical Trials Registry	Free text search (but only searches within titles)	-	27	-	-	Not possible to identify paediatric trials
12	UK pharm. industry (ABPI)	Can select "ALL trials" or free text search (but only searches within titles)	-	110	-	-	Not possible to identify paediatric trials

CI, Confidence interval

^a Approximate number of trials because it was too difficult to carry out a precise count of the number of trials given the site's structure

currently developing a paediatric search filter and website in order to achieve this. At the European level, the European Medicines Agency (EMA) is also attempting to improve accessibility to paediatric data, as required by the Paediatric Regulation [19], by making data on paediatric trials in its EudraCT database publicly accessible. These data will also then be made available through the WHO portal.

Most of the registers included in this review had public/government support, and this may in part be due to the motives behind the creation of registers. The main goal of public service registers is to make information as accessible as possible, while pharmaceutical companies may create registers only to fulfill public “obligations” and are, for obvious reasons, reluctant to disclose their trial data.

The weighted average of paediatric trials in the registers was 15% and the percentage of published articles involving paediatric clinical trials resulted in was 25% (range 4.8–33.3%). There are large constraints involved in this comparison, including potential publication bias, in which it is probable that many of the trials carried out were never published. It is therefore difficult to draw a conclusion as to whether or not the proportion of paediatric studies included in trial registers is representative of the actual number of paediatric studies performed. However, the registers seem to represent fewer paediatric trials than those reported in the literature. These data are difficult to comment on because, aside from possible publication bias and duplicate trials, the presence of paediatric trials in the registers depends on the type and aims of—and participation in—each register. Interest in paediatric studies has been increasing in the last few years and together with the new Paediatric Regulation in Europe that is generating additional and more useful trials and the requirement that these be registered, it is hoped that these studies will be published and become public knowledge.

One of the limits of this study is that it had to rely on the limited search facilities of the different registers. For this reason, although all possible efforts were made to identify all paediatric trials and to exclude adult trials from each register, a precise result could not be guaranteed.

In general, this review found that numerous registers exist, but that few are open to trials involving any therapeutic area, few are easily searchable and few provide detailed trial information. In the last few years, with the efforts placed by groups such as the ICMJE and WHO, clinical trials have been registered in greater numbers and in fewer, selected registers. The situation is still not optimal, but the direction the world is moving in seems likely to bring about worldwide access to dependable research data and results. It would be interesting, in future research, to analyse the paediatric research situation in terms of

therapeutic areas addressed by the trials—an analysis that is not currently easily practicable given the limited search facilities of the different registers.

Conflicts of interest None.

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