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Clinical Trials in Children and Healthy Volunteers. Quality and Characteristics of Notifications Reviewed by the Regulatory Agency in Finland

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Aim: **To investigate the quality and characteristics of notifications on clinical drug trials to be conducted in children and adult healthy volunteers in Finland.**

Methods: **All clinical drug trials involving children and healthy adult volunteers reviewed by the regulatory agency in Finland during the years 1992, 1994, 1996, 1998 and 2000 were analysed. The notifications were classified into the following categories: trials with no objection to commencement, number and type of questions raised, profile, phase and type of study, and trial design.**

Results: **Altogether 352 trial notifications were analysed. Children were involved in 27% of the trials and healthy volunteers in 73%. Most of the trials in children were phase III (53%), placebo-controlled studies with/without active controls (34%) while most trials involving healthy volunteers were phase I studies (70%) with a cross over, placebo-controlled design with/without active controls (42%). Investigations on new chemical entities (34% children; 23% healthy volunteers) and products that did not have marketing authorisation (55% children; 63% healthy volunteers) were most common. The regulatory agency had no objections or questions about 47% (children) and 74% (healthy volunteers) of the notifications. Respectively, 49% (children) and 24% (healthy volunteers) of the trials were permitted to begin after further clarification, while 3% and 2% were rejected. Most questions concerning the trials involving children dealt with the information provided to the study subjects (80%), while safety issues (47%) were most important in the trials involving healthy volunteers. Only a few of the trials (8% children; 5% healthy volunteers) were later cancelled or discontinued.**

Conclusion: **6.6% of clinical trials in Finland involve children. Trials in children raise questions twice as often as trials in healthy volunteers. The contents of the documents provided to the authority, especially those concerning subject information (children) and safety (healthy volunteers), should be improved to gain better compliance with Good Clinical Practice.**

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Introduction

There is an increasing need to conduct clinical drug trials in special populations, especially children[1-3]. As the majority of trials are carried out in adult subjects, knowledge about the efficacy, safety and kinetics of drugs in special populations, e.g. minors, pregnant or breast-feeding women, handicapped or elderly subjects, is scanty[4,5]. However, children (0 to 14 years) account for 30% of the total population globally and 20% in the European Union[6,7]. Over 50% of the new drugs coming to the market and administered to children have been estimated to lack sufficient clinical testing or instructions for paediatric patients[7-9]. Therefore, these drugs are used off-label or are unlicensed, and their usage is extrapolated based on the results of adult trials[2,8, 9]. To obtain sufficient information for treating children safely and effectively and to avoid leaving them as therapeutic orphans, the need to carry out clinical trials in them has been increasingly emphasised[9, 10]. Thus, in Europe, the United States and Japan, the authorities encourage pharmaceutical companies to carry out clinical trials in children by issuing new regulations or initiatives, incentive programmes and international guidelines[7,11,12].

Children account for 18% of the Finnish population[6]. According to the Finnish law on medical research, children are accepted as study subjects only if similar scientific results cannot be obtained by using other subjects, and only minimal risk or burden is acceptable in the case of children. Additionally, children, or any other similar group of persons, including pregnant or lactating women or prisoners, should derive direct or specific benefit from the trial they participate in. Otherwise, they should not be recruited to participate[13]. Finland is involved in approximately 9% of the total number of ongoing clinical drug trials (phases I to III) worldwide[14]. Annually, approximately 300 new clinical drug trials are reported to the Finnish drug regulatory agency, the National Agency for Medicines (NAM). The number of subjects participating in the trials has varied between 32, 000 and 61, 000 from 1995 to 2002[15].

As far as we have been able to ascertain, not much data are available regarding the regulatory authorities' reviews of submitted clinical drug trial applications/notifications or the number and characteristics of trials being carried out in children or other special populations. The aim of the present study was to investigate the number and type of deficiencies NAM noted and the questions they posed to the study sponsors when reviewing trial protocols involving children as study subjects during the 1990s. Because the majority of subjects other than adult patients were adult healthy volunteers this group was included in the study as a reference group. A further aim was to investigate the characteristics of these trials, i.e. the number, type, design, phase, therapeutic area and duration of the clinical trials and the trial centres, to obtain a more detailed view of the clinical trials being carried out in children in Finland. Additionally, the effect of Good Clinical Practice (GCP), e.g. The International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP)[16], on the quality of the notifications filed in the 1990s was reviewed.

Methods

Notification process in Finland

Up to and including the year 2000, ethical approval had to be obtained before submitting a trial protocol to NAM. From 2001 onwards, the trial protocol was submitted simultaneously to NAM and the ethics committee[17]. Notification to NAM had to be submitted before the beginning of a clinical drug trial. The notification requirement applies to medicinal products that do not have marketing authorisation and, in special cases, also to marketed products, when, for example, a new indication in a special subject population is assessed or a controlled or multicentre trial is arranged. If no objections are raised within 60 days of the submission, the trial can be started. In practice, the notification

procedure is equivalent to tacit authorisation, which the NAM has full powers to revoke before it takes effect. Thus, the fact that no objection has been raised by NAM can be construed as tacit authorisation. If the submitted documents are not valid, the NAM may ask for additional information, request amendments to be made in the trial protocol or refuse permission. Whenever a trial is suspended, prematurely terminated or completed and whenever any relevant changes occur during the study, the NAM should be informed. Serious adverse events and protocol amendments must also be reported. Within 90 days of the completion of the study, the NAM must be notified, and a report of the results of the trial must be submitted within one year[17].

Notifications to be studied

The present study material consisted of the clinical trial notifications concerning children and healthy volunteers, as trial subjects, submitted to the NAM during 5 years: 1992, 1994, 1996, 1998, and 2000. Trials including both children and/or healthy volunteers as well as adult patients in the same study were included. Data collection every two years was considered to represent the 1990s longitudinally and comprehensively, as the GCP guidelines were implemented during this decade. Altogether 1, 437 notifications were submitted to the NAM during these 5 years, of which 352 trials involved children and healthy volunteers and 10 trials involved elderly subjects. The sample size enabled us to identify possible developments in the quality of notifications and the characteristics of trials.

Our study protocol was presented to the NAM, and approval was obtained. Approval to collect more detailed data regarding the trials carried out on their premises was also obtained from each of the five Finnish university hospitals, i.e. the university hospitals of Helsinki, Kuopio, Oulu, Tampere and Turku. To guarantee confidentiality, data collection was carried out by a designated person from the NAM.

Data collection, entry and statistics

The data for the years 1992 to 1998 were derived from the data collected earlier for another purpose[18]. The retrospective investigation and data collection concerning the year 2000 were carried out from January until March 2002. Most of the data had been computerised by the NAM at the time of submission. The non-computerised data (i.e. trial design and number of subjects in international trials), the notifications and related documents were thoroughly examined, and the data were collected manually. Manual data collection was only done from the notifications of 136 trials, i.e. two fifths of the notifications, carried out in the five university hospitals in 1992 to 2000.

An Excel format database was received from the NAM and converted into SPSS format (SPSS for Windows programme version 11.0.1, SPSS Inc., Illinois, United States). The manually collected data were typed on the data collection forms by a designated person from the NAM and then entered into the SPSS computerised database. All data were anonymous, i.e. neither the medicinal product under investigation, nor the investigator nor the sponsor could be identified. After the database had been edited, it was analysed with the computer programme. The groups of children and healthy volunteers were analysed in detail and the results compared. This paper reports descriptive statistics and cross-tabulations of the characteristics of the trials as well as their scientific and ethical validity.

Results

Number of trial notifications and subjects

During 1992, 1994, 1996, 1998, and 2000, the NAM reviewed 352 clinical trial notifications concerning children and healthy volunteers out of the total number of 1, 437 clinical trials reported to them. There were 95 paediatric clinical trials (27%) and 257 involving healthy volunteers (73%). The annual numbers of notifications on paediatric trials ranged from 12 to 25 (4% to 9% of the total number of notifications) while the number of trials in healthy volunteers ranged from 19 to 75 (7% to 24%). Trials in children have been increasing since 1994, while trials in healthy volunteers have been decreasing since 1996 (Table 1).

Trial phase, design, object and duration

The majority (53%) of studies in children were phase III trials, and the other studies were phase IV (23%), phase II (21%) or phase I trials (3%). Most studies (70%) in healthy volunteers were phase I trials, and the other studies were phase IV (14%), phase III (9%) or phase II trials (8%). Cross-over, placebo-controlled trials with or without active controls were the most common trials in healthy volunteers (42%), while placebo-controlled trials with or without active controls in parallel groups were most common in paediatric populations (34%).

Most of the trials were investigations of new chemical entities (34% children; 23% healthy volunteers), trials in a new subject group (20% children) or drug interaction trials (19% healthy

Table 1. Number of notifications of clinical trials in children and healthy volunteers reviewed by the Finnish regulatory authority (the National Agency for Medicines)

	Number of studies		
Year	**Children**	**Healthy volunteers**	**Total number of all trials**
1992	14	46	278
1994	12	60	296
1996	20[a]	75	309
1998	25[b]	57[c]	291
2000	24[a]	19	263
Total	**95 (27%)**	**257 (73%)**	**1,437**

[a] *One trial included both children and adult patients.*
[b] *Three trials included both children and adult patients.*
[c] *One trial included both healthy volunteers and adult patients.*

volunteers), and they were carried out on products that did not have marketing authorisation (55% children; 63% healthy volunteers). The trials mostly involved products with anti-inflammatory action or for nervous and respiratory system diseases in children, or nervous and cardiovascular system diseases in healthy volunteers. More than two thirds of the trials in children were completed in less than twelve months. 27% of the paediatric trials were completed within six months and 44% lasted between seven and twelve months. 82% of the trials in healthy volunteers were completed within six months. The median number of children treated in clinical trials in Finland was 44 (range 5 to 30,000) and 13 in the case of trials in healthy volunteers (range 5 to 450). Most of the trials (57% children; 97% healthy volunteers) were national. Regarding international trials in children conducted in the university hospitals, the median number of paediatric subjects in the trials was 300 (range 30 to 15,000). Out of the 62 trials in healthy volunteers conducted in university hospitals, only two were international.

Trial centres and sponsors

Most studies were single-centre trials (54% children; 98% healthy volunteers). In general, university hospitals (72%) and private clinics (19%) were most commonly involved in the paediatric trials, the other trial centres being central hospitals and health care centres (16% each), district hospitals and health care centre hospitals (8% each), university departments (7%), community institutions (5%) or unspecified (8%). Most of the trials in healthy volunteers were carried out in university departments (29%) and university hospitals (24%), and the rest in community institutions and private clinics (3% each), or unspecified centres (42%). Most of the trials were sponsored by pharmaceutical companies (78% children; 66% healthy volunteers), while the rest were investigator-initiated studies.

Regulatory authority's (NAM) review

During the 1990s, until the year 2000, an average of 47% of the applications pertaining to children and 74% of those pertaining to healthy volunteers were accepted without any questions. In the paediatric trials, half of the notifications had to be amended either once (41%) or twice (8%). Regarding the trials in healthy volunteers, one quarter of the notifications had to be amended either once (23%) or twice (2%). Only 3% (children) and 2% (healthy volunteers) of the notifications were not approved, i.e. they could not be evaluated because the notifications were deficient for reliable evaluation. Thus, additional data/documents were asked for from the applicants but they instead cancelled the trials (Table 2). Out of the 92 permitted paediatric trials, five (5%) were later cancelled or prematurely terminated by the applicant, and three trials (3%) were not approved due to the trial sponsor not responding to the questions at all or withdrawing the notification. For the 253 permitted trials in healthy volunteers, the respective figures were nine (3%) and four (2%) (Table 3).

The questions raised by the NAM mostly concerned the subject information sheet (80%) in paediatric trials. The number of questions concerning this issue has been increasing markedly since 1996. Subject information issues were less often discussed in the trials involving healthy volunteers (38%), but safety issues were more common (47%) than in paediatric trials (26%). Administrative issues (10% children; 29% healthy

Table 2. Decisions of the Finnish regulatory authority (the National Agency for Medicines) on notifications regarding clinical trials in children reviewed from 1992 to 2000

	Number of studies					
Year	**Submitted**	**Approved without change**	**Approved after one modification[a]**	**Approved after >one modification[b]**	**Not approved[c]**	**Approved but discontinued /cancelled[d]**
1992	14	8 (57%	5	1	0	1
1994	12	8 (67%)	4	0	0	0
1996	20	12 (60%)	7	0	1	3
1998	25	10 (40%)	12	2	1	1
2000	24	7 (29%)	11	5	1	0
Total (%)	**95**	**45 (47)**	**39 (41)**	**8 (8)**	**3 (3)**	**5**

[a] *Extra documents or equivalent were needed before the final approval.*
[b] *Further questions raised after the applicant's response to the first request for modification.*
[c] *Major amendments or more supporting data were needed, or the documents could not be evaluated because of deficiencies. The queries were not responded, sponsor cancelled the trial.*
[d] *Sponsor discontinued/cancelled the trial after the approval.*

Table 3. Decisions of the Finnish regulatory authority (the National Agency for Medicines) on notifications regarding clinical trials in healthy volunteers reviewed from 1992 to 2000

	Number of studies					
Year	**Submitted**	**Approved without change**	**Approved after one modification[a]**	**Approved after >one modification[b]**	**Not approved[c]**	**Approved but discontinued /cancelled[d]**
1992	46	37 (80%)	7	1	1	1
1994	60	42 (70%)	17	1	0	0
1996	75	53 (71%)	18	2	2	4
1998	57	44 (77%)	12	0	1	4
2000	19	15 (79%)	4	0	0	0
Total (%)	**257**	**191 (74)**	**58 (23)**	**4 (2)**	**4 (2)**	**9**

[a] *Extra documents or equivalent were needed before the final approval.*
[b] *Further questions raised after the applicant's response to the first request for modification.*
[c] *Major amendments or more supporting data were needed, or the documents could not be evaluated because of deficiencies. The queries were not responded, sponsor cancelled the trial.*
[d] *Sponsor discontinued/cancelled the trial after the approval.*

volunteers), including missing forms, approvals by ethics committees, and questions regarding the trial protocol (18% children; 15% healthy volunteers) were raised as well (Figures 1 and 2). Many (43% children; 42% healthy volunteers) of the questions pertained to several issues simultaneously, i.e. addressed a combination of items, e.g. subject information and subjects' safety, trial protocol or administrative issues. Investigator-initiated trials raised more queries (62% children; 35% healthy volunteers) than trials sponsored by pharmaceutical companies (49% children; 21% healthy volunteers).

Detailed figures about the number of notifications concerning whether or not the trial was completed were not available.

Discussion

The scientific and ethical validity of clinical trial notifications on children and healthy adult volunteers, reviewed by the regulatory authority in Finland in the 1990s was investigated. More than half of the notifications on paediatric trials were not valid, required modifications either once or twice or were rejected. Additionally, the proportion of approved notifications has been

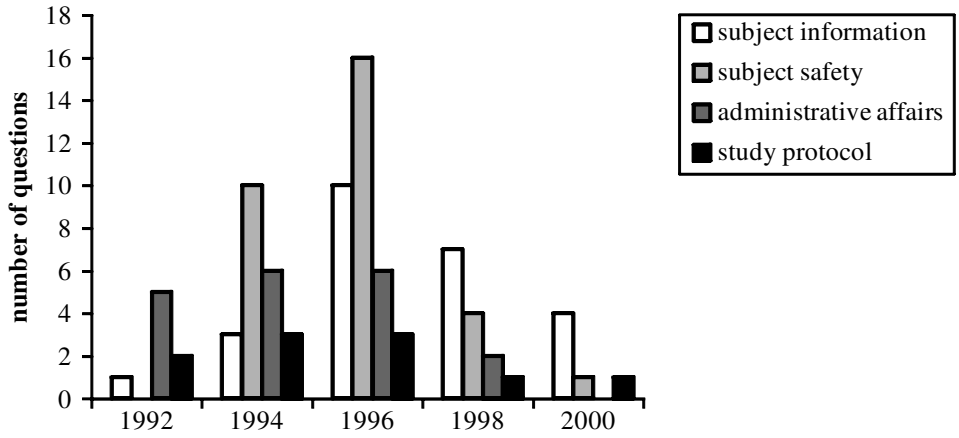

Figure 1. Issues involved in the questions raised by the National Agency for Medicines on clinical trial notifications on healthy volunteers reviewed from 1992 to 2000 in Finland.

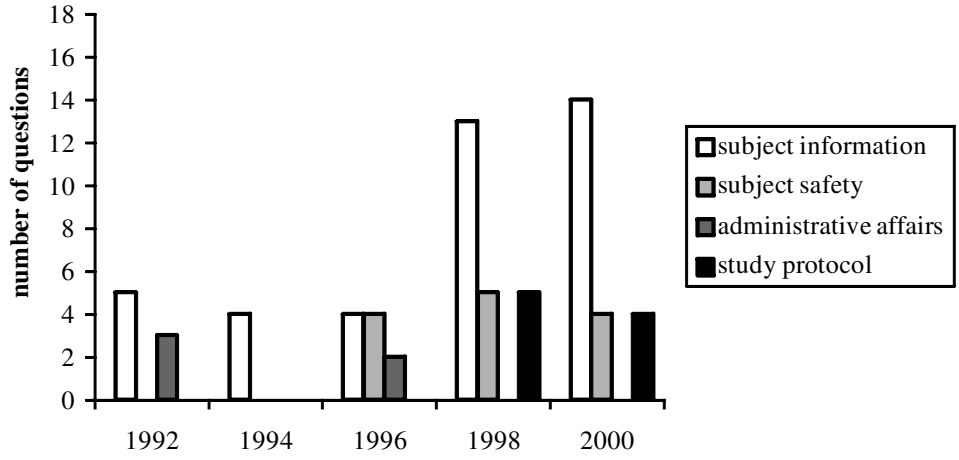

Figure 2. Issues involved in the questions raised by the National Agency for Medicines on paediatric clinical trial notifications from 1992 to 2000 in Finland.

decreasing since 1994. The proportion of approved notifications on healthy volunteers remained unchanged during the 1990s, and three quarters of the trials reviewed were valid and required no modifications, while the rest had to be amended once or twice or were rejected.

Most paediatric trials involved anti-inflammatory agents and products for nervous system and respiratory system diseases. More than two thirds of the trials lasted less than one year. Thus, most paediatric trials lasted as long as trials in adult patients[18] but longer than trials in healthy volunteers which usually lasted for six months or less. Subject information issues were the most common queries raised in paediatric trials and the second most common queries raised in the trials in healthy volunteers. The importance of these issues has been markedly increasing since 1996 in paediatric trials while it has been decreasing in the trials in healthy volunteers. Though the number of paediatric trials has also increased since 1996, this does not alone explain the high number of questions. One reason for the increased number of questions after 1996 could be the stricter rules and the adoption of the GCP principles. As children constitute a vulnerable subject group[9], and informed consent is often neither appropriate nor legally possible, i.e. only assent to participate and parental right to consent[19], it is evident that these issues raise questions increasingly often.

Informing children is naturally more difficult than informing adults. However, the results show that these documents in general, in the case of trials either in adults or children, need improvement to avoid GCP violations. Deficiencies in the subject information sheet have represented the greatest problem with respect to GCP compliance[20,21] and violate one of the most important principles of GCP to protect subjects' rights and well-being. The need for improvements has been reported by us earlier in Finland[18] and by other authors internationally[22,23]. While the number of new paediatric trials started in Finland is steadily

increasing, parallel to the international trend, the submitted documents should be better prepared to comply with GCP, to avoid an increase in the number of questions and, thus, delay in the review process. Additionally, the number of further questions raised after the applicant's response to the first request for modifications has increased since 1998. As, based on the European Directive on GCP[24], the applicant may amend the content of the notification only once, there is an increasing need to improve the content of notifications.

Subjects' safety issues were common especially in the trials in healthy volunteers, where half of the questions pertained to these issues. This is not surprising in view of the types of trials, i.e. typically phase I studies of new chemical entities or drug interaction studies. According to the regulatory authorities' review, clinical trials in children have been planned equally well as trials in adults, though questions regarding study protocols have been increasing since 1996 in paediatric trials. Generally, the high frequency of queries regarding subject information and safety is somewhat surprising, given that from 1992 to 2000, the ethics committees had to review and approve the trial documents before they were submitted to the regulatory authority. This raises a question as to whether the ethics committees have done their job with sufficient care. Regarding both issues, ethics committees play a crucial role in protecting the children participating in clinical trials and should have members experienced in working with children, which has been highlighted by other authors, too[9, 25].

Fair subject selection is a prerequisite for ethical clinical research[26]. However, there is a dogma that it is unethical to test drugs in children[27]. On the contrary, it has been questioned whether it is ethical to prescribe untested drugs to children[2,8]. In a European study, 67% of children admitted into hospital wards received drugs prescribed as unlicensed or off-label, and 39% of the prescriptions were off-label[2], thereby increasing the risk of adverse drug reactions[1]. To ensure that children are not exposed to unnecessary risks, clinical trials are needed to determine the appropriate doses for each age level of children[2]. In this way clinical decision-making can be based on direct findings. The issue of extrapolation of the results does not concern only children but also women, elderly subjects, members of racial or ethnic minorities, and other special populations[28]. Populations at risk for a certain disease or receiving treatment should be represented in appropriate clinical trials[26, 28], but this has been complicated for a number of reasons, including practical, economic, legal, and ethical issues[7, 9, 10, 29, 30]. However, based on the results of our study, trials in children have been increasing in Finland.

In conclusion, the results show that a considerable proportion of the documents submitted to the authority should be prepared more carefully, especially concerning subject information in paediatric trials and subjects' safety in trials involving healthy volunteers, to gain better compliance with GCP.

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