ABSTRACT. A considerable number of patients have to be recruited in a clinical trial to obtain solid results. In pediatric studies, patient recruitment is frequently problematic. In the simple common childhood illnesses, the number of recruitable patients is certainly large, but they may be hard to reach, and the imbalance between potential benefit and inconvenience of participation may reduce motivation to enroll. In severe diseases, the balance may be right, but the available number of patients may be small. Good communication with the child and family, as well as the motivation of colleagues to admit, is another key element in success. Proper study design, including realistically identified sources of patients, reasonable inclusion, and exclusion criteria, also are required.

ABBREVIATIONS. EU, European Union; IRB, institutional review board; UTI, urinary tract infection; GP, general practitioner.

Patient Recruitment—European Perspective
Kalle Hoppu, MD, PhD

PREREQUISITES TO RECRUITMENT
National laws, international conventions, and EU directives and guidelines direct and regulate biomedical research. The European documents on biomedical research generally (The Convention on Human Rights and Biomedicine by the Council of Europe) and clinical trials in children specifically (Guidelines on Clinical Investigation of Medicinal Products in Children) recently have been revised and are undergoing final stages of approval. They require that a child undergoing research should stand to obtain some benefit, except under very specific conditions. The risk of any intervention must not be disproportionate to the potential benefit.

An established condition for enrollment of children is parental consent, in writing. The Convention states that, “the opinion of minors should be regarded as an increasingly determining factor in proportion of their age and capacity for discernment.” Financial or other inducements are prohibited, but reimbursement for costs are allowed. These principles follow present internationally accepted standards in effect banning the use of children as “healthy volunteers” in research. Only pediatric patients can be recruited for clinical trials, except in studies on vaccinations and similar preventive measures.

The primary principles described above are generally accepted in Europe. The sovereign European countries may, however, to some degree vary in the interpretation of the conventions, and legislation may reflect national considerations.

DEMOGRAPHICS
Europe is populated by ~800 million people. In the 15 countries of the EU, ~17.8% of the 372 million inhabitants are younger than age 15 years. The health of the European children is generally good, in a way diminishing the number of potentially available patients for pediatric clinical trials.

The great majority of European people are of Caucasian origin, but the number of non-European immigrants has been increasing for some time. Genetic differences in incidence of many diseases exist within Europe. For example, in Finland thalassemia is found only in immigrants and cystic fibrosis is extremely rare, practically excluding clinical research of these diseases. On the other hand, there is a Finnish type of congenital nephrosis, a rare autosomal recessive and always fatal illness unless renal transplantation is undertaken. In Finland, the number of children requiring kidney transplantation before 2 years of age is exceptionally high, giving an opportunity and obligation to study immunosuppressive therapy in this age group.

SOURCES OF PATIENTS
The health care systems in European countries are different, with varying degrees of private and public funding. Children usually are recruited to a clinical trial by physicians with special groups of patients or by referral from primary care. The group of physicians caring for children is different in different countries. Of the ~40 000 pediatricians in the EU, 30 000 work in primary care and 5000 in tertiary care. For example, in many southern European countries,
the pediatrician is the physician caring for children in primary care; in the United Kingdom, it is the general practitioner (GP). This is reflected in the number of pediatricians in Italy (8000) and in the United Kingdom (1000), both countries with ~60 million inhabitants.

National and local registers of patients can be of help in finding patients to recruit and sometimes even for contacting families directly when recruiting from special populations. Potential benefit being a condition for pediatric clinical trials, in some cases cautious “advertisement” directed either to other groups of health care workers such as well-baby clinic or school health personnel or to parents also may be used. Recruitment from sources other than physicians is essential in trials involving common conditions usually treated at home.

RECRUITING CHILDREN INTO CLINICAL TRIALS—A FINNISH PERSPECTIVE

In Finland, before recruitment of children to a clinical trial can begin, the study protocol has to pass through a local institutional review board (IRB) and a review by the National Agency for Medicines. No ethical committee with overregional authority or coordinating body for IRBs exists. The IRBs do not necessary agree on what can be accepted as minimal burden or appropriate risk, and it is possible that a protocol for a pediatric multicenter trial is accepted by one IRB and rejected by another. The National Agency for Medicines reserves 60 days for inquiries or to veto an investigation plan, but it does not give definite approval. The Agency has shown a pragmatic and proper attitude toward pediatric clinical trials.

Finland (population, 5 million) has a public health care system. In primary care, children usually are cared for by GPs. Pediatricians are primarily hospital-based. Treatment of less common diseases or conditions requiring specially trained personnel or exceptional equipment is well-centralized. A nationwide system of well-baby clinics and school health care cover practically the entire child population. Many good national registers exist to help find groups of patients for recruitment or to trace patients and their addresses.

One of the weaknesses of the Finnish public health care system is a built-in difficulty for a patient to meet the same doctor regularly, particularly in the research-oriented university hospitals. Some corrective measures have been initiated, but still the promise of a steady patient–doctor relationship is a good incentive for enrollment of pediatric patients to studies requiring follow-up. Finnish people are to a major extent, for some reason, willing and capable of following protocols and exceptionally motivated to follow up. This helps retention in clinical trials and compensates to some extent for the limited size of the child population when recruiting subjects for clinical trials. Combined with the primarily positive image medical research still has in Finland, enrollment of children into trials with reasonable protocols is not overly difficult.

CASE DESCRIPTIONS

Pharmacokinetic Study of Trimethoprim

In the 1980s, we recruited 18 children, 1 to 3 or 8 to 10 years of age, with acute urinary tract infection (UTI) to determine the pharmacokinetics of trimethoprim. The mostly ambulatory patients were studied for 3 hours after the first dose, which was administered immediately after the diagnosis was established. The treatment was continued for 10 days, and the children were admitted to the hospital for the last dose and a pharmacokinetic study lasting 24 hours. Children were recruited from the outpatient department of our hospital and from outside with advertisements directed to the GPs in the greater Helsinki area. Colleagues were asked to admit patients with suspected UTI who filled the age criteria. The children were recruited by the investigator immediately after the diagnosis was established. He followed the patients for 6 months after the UTI and was available to take care of any other medical problems appearing during that time.

As usual, patient enrollment was slower than expected, primarily because fewer patients than expected were available for recruitment. This was overcome with slight widening of the original age limits and repeated reminders to the GPs and nursing staff of our outpatient department. Exact numbers are not available, but patient refusal was primarily related to the somewhat inconvenient requirement to stay for an additional 3 hours after the diagnostic process, which often already had taken several hours. It is questionable whether the results of the first phase of the investigation, the obtaining of \( C_{\text{max}} \) (maximum plasma/serum concentration) and \( t_{\text{max}} \) (time of maximum plasma/serum concentration after dosing), were worth the recruitment problems encountered.

Pharmacokinetic Study of Cyclosporine A

Renal transplantation to young children with congenital nephrosis was started at the end of the 1980s in our hospital. At that time, no pharmacokinetic data on cyclosporine A was available in the relevant age group (1–3 years old). Theoretically, it was likely that these children needed larger weight-corrected doses than did older children or adults to obtain recommended cyclosporine A blood levels and adequate immunosuppression.

A protocol was set up to study the pharmacokinetics of cyclosporine A after both a single oral and an intravenous dose. The study was included in the pretransplantation routines and the data used to calculate individual dose recommendations to be utilized at the time of the transplantation. This arrangement held such promise of direct benefit to both the patient and the transplant physicians that all eligible children could be recruited without difficulty.

The entire procedure was, in fact, perceived by the transplant physicians as so valuable that it was continued after the original investigation was finished. The individual pharmacokinetic study has became standard procedure for all children scheduled to undergo renal or heart transplantation at our hospital.
The pediatric transplantations in our country are handled by a single center, making all patients available for recruitment, and at present 115 have undergone such a study.

**Controlled Clinical Trial of a Bronchodilator + Antitussive Combination (Unpublished)**

On the initiative of a pharmaceutics company, we set up an efficacy study of a bronchodilator + antitussive combination in the treatment of acute cough in children. The aim was to compare the efficacy of an evening dose of either active drug or placebo during the child’s sleep. The efficacy variables were reduction of cough frequency and intensity, and time of undisturbed sleep. Sophisticated equipment using filtered acoustic signals and movements on a static charge sensitive bed was used. All the equipment was stationed either outside the bed or under the ordinary mattress. The recordings were made on two consecutive nights at home. A study nurse set up the equipment on both evenings. The family had to administer the drug in the evening, and the child had to sleep in his or her own bed. The present acute respiratory tract infection was treated by the same investigator, and the families were given access to her mobile phone number for consultations.

Children were recruited from the outpatient department of one hospital and with advertisement directed to the GPs in the Helsinki area. Enrollment proceeded slowly. Small adjustments to the inclusion criteria were made and verbal and oral reminders to colleagues issued. Direct advertisement targeting parents was added in the form of circulars distributed to well-baby clinics in the area. Finally, the recruitment target of 30 patients was met. The study proved inconclusive, primarily because of unreliability of the monitoring equipment in the home setting.

Recruitment was problematic, although the symptom was very common, and we had invested considerable effort to make the study as easy as possible for the child and family. The requirement of a relatively stable phase of cough (minimum 3 days) in the inclusion criteria and exclusion of any child suspected of having airway hyperreactivity was partly responsible. The limited benefit the child and family conceivably could obtain from participation compared with all the inconvenience probably was one of the primary reasons for the low interest.

**Optimal Drug Treatment of Recurrent Headaches and Migraine in Children**

Ambulatory headache clinics were set up in three Greater Helsinki area (900 000 inhabitants, ~170 000 younger than age 15 years) hospitals especially for this study. The investigator cared for all pediatric patients suffering from headache referred either to the hospitals or from within the hospitals. A run-in period was used to verify that the patients were eligible, suffered migraine or migraine-like disorder and did not have a satisfactory treatment already, and filled inclusion criteria such as sufficient frequency of attacks and ability to perform evaluation of pain severity at home as required. Eligible children filling inclusion criteria were recruited to one of three clinical trials at a time. If a satisfactory treatment was not found, the child could enter the next trial, if the inclusion criteria still were met. In the trials, a single attack of migraine was treated at home with oral ibuprofen or acetaminophen, nasal dihydroergotamine, or oral sumatriptan in a double-blind, randomized crossover design and with placebo control. The enrollment of patients (Fig 1) met our expectations reasonably well. The good overall efficacy of the drugs of the first study, ibuprofen and acetaminophen, led to slower-than-expected enrollment in the later trials.

We used both verbal and written advertisement to the GPs and pediatricians in the area. A beneficial factor was that although migraine is the most common type of recurrent pain in children, affecting 2.5% to 19%,6 no active interest for the treatment of children with migraine had existed in our area. The promise of a specialized clinic with a continuous patient–doctor relationship and new hope for effective treatment were powerful motivations for recruitment for the children and families. Which additional factors might have helped in the motivation of our colleagues in the area is difficult to determine, but the rate of referrals generally met our expectations without extra efforts. The decision to have the investigator, rather than the patients, move among the three hospitals was a good one. The hospitals belong to separate organizations and, with this solution, we reduced considerably the problems of funding patient visits and associated investigations.

**CONCLUSIONS**

For solid results, a considerable number of patients have to be recruited in a clinical trial. Innovative study designs can minimize the number of subjects, but in pediatric studies, patient recruitment frequently is problematic. Many factors should be considered (Table 1) to facilitate recruitment into and retention of patients in the trial. With simple common illnesses, the number of potentially recruitable patients is certainly large enough. They may be difficult to reach, and the imbalance between potential
benefit and inconvenience of participation may re-
reduce motivation. With more severe disease, the bal-
ance may be correct, but the available numbers often
are small. Good communication between the patient
and the doctor is in many ways a key element in
recruitment. Other methods of delivering informa-
tion, such as group meetings, have been used with
success.7 Information, communication, and percep-
tion of some benefit also are essential to motivate

TABLE 1. Some Important Factors to Consider When Recruiting
Children to a Clinical Trial

Factors related to the child and family
Perception of a real benefit to the child (no financial or other
inducements allowed)
Good patient–doctor relationship
Clear and correct understanding of what the trial is all about
Factors related to the investigators
Good communication and patient–doctor relationship
Distributing clear and correct information of what the trial is
all about
Factors related to the study design
Inclusion and exclusion criteria reasonable in relation to
availability of patients
Simple for the child and family
Factors related to sources of recruitment
Motivation for a colleague to admit (perception of a benefit to
a child or to him/herself)
Clear and correct understanding of what the trial is all about
Information and reminders

benefits and inconvenience of participation may re-
duce motivation. With more severe disease, the bal-
ance may be correct, but the available numbers often
are small. Good communication between the patient
and the doctor is in many ways a key element in
recruitment. Other methods of delivering informa-
tion, such as group meetings, have been used with
success.7 Information, communication, and percep-
tion of some benefit also are essential to motivate
colleagues to admit children for a trial, and this can
even be the toughest part of patient recruitment.

Patient enrollment almost always seems to take
longer than expected. In addition to the various fac-
tors noted above, a good study design is crucial.
Realistically identified sources of patients and rea-
sonable inclusion and exclusion criteria are required.
For success, it is not exaggerated to use all feasible
measures and sources of patient recruitment in an
effort to avoid overly prolonged enrollment.

REFERENCES

1. Hoppu K. Age differences in trimethoprim pharmacokinetics—need for
2. Hoppu K, Koskimies O, Holmberg C, Hirvisalo EL. Pharmacokineti-
cally determined cyclosporine dosage in young children. Pediatr Neph-
rol. 1991;5:1–4
3. Hämäläinen ML, Hoppu K, Valkeila E, Santavuori PR. Ibuprofen or
acetaminophen for the acute treatment of migraine in children: a ran-
1997;48:3–7
4. Hämäläinen ML, Hoppu K, Santavuori PR. Oral dihydroergotamine in
therapy resistant migraine attacks in children: a placebo-controlled pilot
5. Hämäläinen ML, Hen ML, Hoppu K, Santavuori PR. Sumatriptan in
migraine attacks in children, a randomized, placebo-controlled study.
Neurology. 1997;48:1100–1103
6. Abu-Aref I, Russel G. Prevalence of headache and migraine in school
ment in clinical trial in pediatrics. Therapie. 1991;46:139–142
# Patient Recruitment—European Perspective

Kalle Hoppu

*Pediatrics* 1999;104;623

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/104/Supplement_3/623">http://pediatrics.aappublications.org/content/104/Supplement_3/623</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 35 articles, 0 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/104/Supplement_3/623.full#ref-list-1">http://pediatrics.aappublications.org/content/104/Supplement_3/623.full#ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Pharmacology <a href="http://classic.pediatrics.aappublications.org/cgi/collection/pharmacology_sub">http://classic.pediatrics.aappublications.org/cgi/collection/pharmacology_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>
Patient Recruitment—European Perspective
Kalle Hoppu
*Pediatrics* 1999;104;623

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/104/Supplement_3/623