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Recruiting Children to a Clinical Trial

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Abstract

Objective: *To determine the reasons for parents and children declining to enter a clinical trial.*
Design: *Prospective study of patient recruitment to a clinical trial over a period of one year.*
Setting: *Children's day case ward in a children's hospital.*
Subjects: *Children presenting for venepuncture to a day case ward.*
Main Outcome Measure: *Number of children recruited to the trial and reasons for declining to enter.*
Results: *One thousand and seventy four children presented for venepuncture to the unit when the research nurse was present. Four hundred and ninety one children satisfied the inclusion criteria and were approached by the research nurse, of whom 43 were recruited. The main reasons for declining entry to the trial were time, the desire not to participate in a clinical trial and a request from the child for use of treatment previously received.*
Conclusions: *Recruitment of children to clinical trials may be difficult. The difficulties of recruiting children to clinical trials need to be appreciated by all interested parties.*

Key words: Children – Clinical trials – Recruitment – Consent

Introduction

There is increasing interest in clinical trials in children[1]. Clinical trials are important to ensure both the efficacy and the safety of medicines used in children. Studies in the UK and Europe have shown that many medicines routinely used in children in hospital are not licensed for such use[2–4]. Health professionals, the pharmaceutical industry and politicians have all expressed their concern at this unsatisfactory situation. Pharmaceutical companies are being encouraged to carry out clinical trials in children of medicines that are likely to have a significant therapeutic benefit on them. With children it is crucial that clinical trials involve health professionals who themselves have direct clinical contact with children. There is little data available regarding the difficulties involved in clinical trials in children. We wish to report our findings on the difficulties of recruiting children into one particular clinical trial.

Methods

Over a 12-month period a clinical trial was carried out evaluating a new local anaesthetic agent for

children undergoing venepuncture. The study was approved by the Southern Derbyshire Ethics Committee. Children presenting to a day case ward at Derbyshire Children's Hospital for blood samples were approached to take part in the study. The precise details of the trial will be reported separately, but it involved the use of a local anaesthetic, which was to be administered prior to venepuncture. These children previously would not have been offered local anaesthesia because of the time delay involved. The study was a double-blind, randomised, controlled trial involving both active local anaesthetic and placebo. One in three children received placebo. The new local anaesthetic is thought to have a rapid onset of action and therefore venepuncture was carried out three minutes after the application of the local anaesthetic. Thereafter assessments of pain, and also the site of application, were carried out by a research nurse employed specifically for the project. Assessments were carried out pre- and post-dosing, for 15 minutes following venepuncture and thereafter at 1, 8 and 24 hours.

The inclusion criteria were quite detailed in order to ensure the safety of all children in whom the new local anaesthetic agent was being tested. The inclusion criteria were children aged 4–14 years of Caucasian race, ASA class 1–2 with no developmental delay, and without a history of blood or clotting disorders, eczema or keloid formation, or allergy to plasters or local anaesthetics. A parent needed to be present and the child needed to have a satisfactory venepuncture site. The child had to have had no analgesia in the previous 12 hours and no investigational drug or vaccination in the last month. The parents and children were approached by the research nurse, who explained the details of the study to both the parents and the child. The research nurse kept a record of each individual parent and child who was approached, and where consent was declined, the reasons for this were noted.

Table 1. Number of patients not fitting the inclusion criteria

Age	383
Race	50
Child with special needs	37
History of blood/clotting disorders	34
History of eczema/keloid formation	24
No parent present	15
Poor venepuncture site	14
Taken analgesia in the last 12 hours	14
Allergy to plasters/local anaesthetics	8
Vaccination in the last month	4
Total	583

Table 2. Reasons for parents and children declining to enter the trial

Time	157
Do not wish to be involved in the trial	74
Child requesting local anaesthetic cream previously used	70
Parents not wanting the child to have local anaesthetic	31
Child unhappy to take part in trial	28
Child upset or shy	24
Difficulties in arranging home visit	20
Language issues	13
Previously entered the trial	9
Bruising on site of venepuncture	6
Child felt faint/fainted	6
Skin problems over venepuncture site	4
Not approached	3
Child requested fingerprick blood test	2
Child hungry (fasting blood test)	1
Total	448

Results

Over a period of 12 months, 1074 children presented for venepuncture to the unit when the research nurse was present. Over half of these were excluded automatically, as they did not fit the inclusion criteria. The precise reasons why they were excluded are listed in Table 1. Four hundred and ninety one children were considered suitable for the study and were approached by the research nurse. Forty-three of these children (8.8%) and their parents agreed to take part in the study.

In 448 cases, the parents or the child declined to take part in the trial. The reasons for this are shown in Table 2. Time was the biggest factor, with 157 parents stating that they did not have the time to wait around for further assessments. Pain was not an issue for the majority of children. Seventy children had previously received a local anaesthetic cream and wished this to be applied again. The other children who did not enter the study did not receive any local anaesthetic, whereas children entering the study had a 67% chance of receiving a local anaesthetic. In 74 cases, parents did not want their child to take part in a trial. In a further 28 cases, although the parents were happy, the child was clearly unhappy to take part in the trial. In three cases the research nurse decided not to approach the parents for consent for confidentiality reasons (presence of social workers). Despite minor

Table 3. Monthly recruitment rate

Month	Number of patients presenting for venepuncture	Number recruited	Recruitment rate (%)
October 1998	36	3	8
November	111	4	4
December	48	1	2
January 1999	76	4	5
February	107	7	7
March	82	5	6
April	71	2	3
May	107	3	3
June	112	3	3
July	107	4	4
August	117	1	1
September	68	3	4
October	33	3	9
Totals	1075	43	59

modifications in the inclusion criteria during the course of the study, the monthly recruitment rate never reached more than 9% (Table 3). The overall recruitment rate was 4%.

Discussion

Clinical trials in children are essential in order to ensure that medicines (both new and old) are formally tested for safety and efficacy. The vast majority of parents and children approached were keen to help on the basis that they would improve the management of children in the future. This is consistent with a previous study, which looked at parental reasons for participating in a clinical trial[5]. There are, however, numerous practical difficulties in recruiting children.

There have been very few studies looking at recruitment of children to clinical trials. Two other studies have involved sending a questionnaire to parents of children who had previously been approached to enter a clinical trial[6,7]. Both studies found that safety for their child was the main reason for declining to enter a clinical trial. In the Australian study of a drug for asthma, lack of time was also a major reason for declining to enter a clinical trial[6]. We are unaware of any other study that has prospectively evaluated the reasons for parents declining to enter a clinical trial involving their child.

It is unethical to recruit healthy children as volunteers for a study such as this. This is practical in adults where clinical research organisations and others can advertise for individuals to test a new local anaesthetic and to undergo a venepuncture that is not clinically required. In children, one can only study those children who are to undergo a clinical procedure and thus may benefit from a medicine. In this study, the use of a placebo was felt to be appropriate, as these children previously were unlikely to receive any local anaesthetic agent. The biggest practical problem was the time required to take part in the study. Involvement in any clinical trial increases the time required, as observation is required in terms of efficacy and toxicity. The recruitment rate remained below 10% throughout the study.

To carry out the above mentioned clinical trial, one full-time clinical research nurse was employed for the duration of the study. The costs of carrying out clinical trials vary considerably with the type of product being investigated. With the type of product used in this trial, most of the data required in adults could be obtained from normal volunteers being studied in a phase 1 unit. Such studies are both fast and cost-effective. Clearly it is not possible to use volunteers in studies involving children and the difficulties of recruitment encountered here added considerably to the time for development of the product and, therefore, the costs. The financial costs of carrying out such clinical trials should not act as a deterrent for pharmaceutical companies wishing to evaluate new medicines in children.

It is important that clinical trials in children are planned carefully. Investigators need to be aware that time is an important factor for busy families. It is also important that exclusion criteria are not too tight. The importance of factors affecting the recruitment of children into clinical trials has been emphasised recently both in Europe[8] and the USA[9]. However, there have been few studies looking at the recruitment of children into clinical trials and we feel that this is an area where more research is required.

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