

# Family genetic studies

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## Recruitment issues

The success of any clinical study is dependent on the investigators' abilities to recruit sufficient patients to participate. Consideration of recruitment is important when designing study protocols because by developing complex, detailed inclusion and exclusion criteria, the pool of patients available to include in the study becomes smaller. Having been involved in developing studies from within the pharmaceutical industry, one of us (WL) has worked with over optimistic clinicians convinced they will be able to recruit the required number of patients for a particular study. It is relatively common, however, that studies fail as a result of incomplete recruitment. Information on these failures is impossible to obtain as such studies are never published. Twenty years ago studies were published without appropriate power calculations and with small numbers of patients. Not so today. Recruitment is therefore an important issue as it is acknowledged that even in common diseases such as viral bronchiolitis, investigators may struggle to enrol the appropriate numbers of patients.<sup>1</sup>

Given the trend towards studies with larger numbers of patients, a recent Medline search into recruitment policies related to clinical trials was disappointing. Of 703 articles of possible interest, 93 were studies in children, but many of these addressed issues such as ethics, consent, patient participation attitudes, and recommendations as to how to maintain patients' interest once they had been recruited into the study.<sup>2-4</sup> Others reported issues which were specific to diseases such as cancer.<sup>5</sup> A paediatric growth hormone study in renal failure<sup>6</sup> expressed concern that the bond between families and professionals may have coerced families into agreeing to

the study. The paper also confirmed that the recruitment process was time consuming and needed careful planning.

A recent family study into the genetics of asthma in Stoke caused us considerable recruitment problems; given the dearth of recruitment information available in the world literature, we felt our local experience was worth reporting.

### AIM

Family genetic studies require the participation of at least one child with the appropriate disease, together with both biological parents. Our initial aim was to recruit 100 families having two or more children (aged 7 years or above) with a doctor diagnosis of asthma, and 100 families having one child (aged 7 years or above) with asthma. Within these 200 families we wished to see a spectrum of disease severity similar to that seen in clinical practice. Our aim was therefore to recruit from both primary and secondary care.

### METHODOLOGY

The study consisted of participating families each filling in detailed asthma phenotype questionnaire forms, and then all family members coming to hospital for half a day to undertake skin prick tests, bronchial hyperreactivity tests, and a blood sample for future candidate gene analysis and total IgE concentrations.

Given that asthma is extremely common in childhood, our initial assumption was that we would have little difficulty in recruiting 200 families over a two year period. Indeed, recalculations suggested that 150 families would be sufficient. We first examined our hospital database and identified 672 patients. We then wrote to general practitioners about a further 822

patients we had identified from the community databases, the accident and emergency department files, and from correspondence indicating patients had been discharged back to primary care. To obtain a wide spectrum of asthma disease severity we also posted 14 813 questionnaires to local schools. From three health promotion days held in a local shopping complex, a further 568 children were identified. Others were identified by word of mouth and from media enquiries. In all, initial contact was made with 16 875 children and their parents. A total of 2936 families were identified as potentially suitable, but following direct contact (usually by phone), only 210 fulfilled the inclusion criteria and were also willing to participate.

### AETIOLOGY OF NON-PARTICIPATION

The main reasons for non-participation were:

- The child no longer had symptomatic asthma requiring therapy
- The half day hospital visit; especially if the child needed to miss school
- The child or the father did not want to have a blood test
- Fathers were particularly difficult to enrol, especially if time off work was required
- Some mothers admitted the child or partner was unaware of the child's paternity
- Others were concerned about the possibility of genetic cloning or wished to be paid to participate
- Forty one families agreed to being enrolled in the study but wasted a significant amount of the research team's time by failing to attend several appointments despite clear agreements in writing and by phone beforehand. Within these 41 families were 20 who insisted on weekend appointments, such failures to attend being particularly annoying for the research team.

There were considerable differences in the numbers of families recruited using the different methods (table 1).

**Table 1** Recruitment of the study population by source

Recruitment source	Families identified (n)	Families agreeing to take part (n)	Percentage of identified families (%)	Families completing study (n)	Percentage of identified families (%)
School questionnaire	1356	108	7.95	78	5.75
General practice	822	13	1.58	8	0.97
Hospital database	672	53	7.89	51	7.6
Via media events	68	20	29.4	15	22.1
Word of mouth	12	10	83.3	8	66.6
Health promotion days	6	6		4	66.6

## CONCLUSIONS

Patient recruitment into clinical studies is vital for their success. There is little information in the world medical literature about the difficulties encountered in the recruitment process. Because the needs of both the child and at least one proxy (usually the mother) have to be satisfied, recruitment of children into clinical studies can be more problematic than that of adults. Not all clinical studies need large numbers of patients. The numbers depend on the size of the effect being investigated. However, treatment differences can be relatively small when comparing one therapeutic regime with another, and recent studies in diseases such as asthma have required large numbers of patients to participate, as in the recent CAMP study in the USA.<sup>7</sup>

Family genetic studies require the involvement of at least one affected child together with both biological parents; in diseases such as asthma where the causation is multifactorial, meaningful results are only obtained using large cohorts, with many of the more powerful statistical techniques requiring hundreds if not thousands of individuals.<sup>8</sup> Such studies within family groups help to control for shared genetic and environmental influences, thereby being powerful methods for obtaining genetic information. The requirement of at least one affected child per family and both genetic parents, however, results in recruitment being potentially more difficult than in other types of clinical studies. Additional information can be obtained from some families by including other affected siblings, or indeed including unaffected siblings to act as normal controls. The greater the number of participants requested per family, however, the greater the likelihood that one or more will refuse to take part.

Table 1 shows the differences in family numbers recruited using the different methods. The schools questionnaire provided the largest numbers of participants, the hospital database of patients attending our hospital outpatient clinic was also fruitful. Recruitment from primary care was disappointing, but this method relies on general practitioners or colleagues in primary care being willing to spend time contacting their patients, and although all practitioners were written to before the study commenced, explaining the reasons for the study, some may have not thought the study worthy of prioritisation in their busy daily schedules. Early in the study the research team featured in three radio programmes, three newspaper articles,

and one local television programme. There was no doubt that interest was generated from these, but overall benefit was difficult to estimate given that only 15 additional families completed the study as a direct consequence of media involvement. It was disappointing to note retrospectively that of the 40 families who said they would participate only if their hospital appointment could take place at the weekend, 50% failed to attend despite careful preplanning and agreed dates and times.

Our clinical study team comprised a full time research fellow (FC) and two full time respiratory research sisters, all knowledgeable in research methods and in childhood asthma. During the two year study period, we estimated well over 50% of their time was occupied in effecting recruitment of the families. Given that only 159 of the original 2936 (5%) families completed the study, this sample cannot be assumed to be representative. It is likely to be highly self selected. It can be argued that the professional time of well qualified doctors and nurses may be better spent in other areas of research, or conversely, as stated by Postlethwaite and colleagues,<sup>6</sup> the bond between such professionals and families may coerce some families into agreeing to the study. There have been suggestions that hospitals should employ recruitment officers to aid enrolment into clinical studies.<sup>9</sup> There are, however, complex issues in relation to genetic studies, about which the families require detailed information and explanation. It is probable that well trained specialist doctors and nurses are the most appropriate professionals to communicate this to the families to allow them to decide whether to participate or not.

It is difficult to extrapolate our recruitment issues to studies in other disease areas, but we know of other UK centres undertaking family genetic studies in asthma where recruitment has been problematic (personal communication). As knowledge of the genetic basis of other multifactorial diseases increases, it is likely that there will be an increase in family genetic studies in diseases other than asthma. Problems related to recruitment will differ between diseases and between research centres. The purpose of this article is to highlight that when such studies take place it is likely that recruitment will be very time consuming. During the planning of these studies a clear strategy needs to be developed appropriate to both the disease and the centre where the study is to take place.

## SUMMARY

Family genetic studies require large numbers of families with at least one affected child and both genetic parents agreeing to take part. In Stoke we recruited 159 families over a two year period from 2936 (5%) potential families. Greater than 50% of the professional time of one research fellow and two research nurses was occupied in recruitment. Reasons for non-recruitment were: the child no longer had symptomatic disease; the family could not afford the time to participate; some family members refused blood tests; paternity was in doubt; and there were concerns about genetic cloning. Recruitment varied depending on the strategy used.

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