

Recruiting patients to clinical trials: lessons from studies of growth hormone treatment in renal failure

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Abstract

Issues raised by the recruitment of children to trials of growth hormone treatment for short stature in chronic renal failure are reported. Information needs of parents and children are discussed, the latter should take account of the children's developmental level and anticipated involvement in decision making. When the incidence of certain side effects is low and probably unquantifiable there are particular problems; failure to include these in information sheets may compromise informed consent but inclusion will, at least for some families, make an already difficult decision even more complicated. A process of recruitment is described which attempts to protect against bias and which balances the requirement to impart neutral information with appropriate clinical involvement in the decision to enter the study. Other functions of the recruitment process are identified. Analysis of understanding and decision making demonstrates that good understanding is neither necessary nor sufficient for ease of decision making. The recruitment process was time consuming and needs planning and funding in future studies. Many of these issues are of general importance for trials of treatment in children.

(*Arch Dis Child* 1995; 73: 30-35)

Keywords: clinical trials, growth hormone, renal failure.

When inviting their patients to take part in clinical trials, doctors generally strive to present a simple, neutral, balanced view, in full awareness that they are themselves rarely either neutral or undecided and that the issues are far from simple. As Tobias and Souhami have recently discussed, certain tensions in this situation are novel.¹ On the one hand, we are in particular need of the scientific information from clinical trials (that is, we need the patients to take part in the trials more than ever before). On the other hand, powerful forces reduce the paternalistic power of the physician to make (or strongly advise on) decisions made by patients. Thus we leave the decisions to patients more than we ever did in the past. Treatment trials with children as patients make matters even more complicated, as discussed in the recent British Paediatric Association guidelines.² In this arena, recent trends in legislation^{3 4} tend to increase the weight given to children's own views on, and decisions

about, large areas of their lives (for example, with whom they live, whether they may consent to treatment). Changes in relationships in the health service have encouraged their parents to demand full information and to take responsibility for decision making.

Recently we have had experience of introducing clinical trials of growth hormone to a group of sometimes multiply handicapped child patients at varying stages of chronic renal failure (CRF). While short stature is an unfortunate complication of their illness, it is not a life threatening one, and the treatment (daily growth hormone injection) is intrusive and expensive. Despite this an improvement in growth, if without significant drawbacks, would be welcomed by the patients. At present the effect of growth hormone treatment on growth in patients with CRF is uncertain and merits examination in a clinical trial. To be scientifically valid, the treatment trial should be offered to all the patients meeting the entry criteria without preselection based on social consideration or intellectual ability.

The Kabi Pharmacia trials of growth hormone in children with CRF and short stature were set up to evaluate the physical benefits of treatment with growth hormone in children with CRF, but also afforded an opportunity to assess psychological consequences, in the broadest sense, for the children and their families. Preliminary results of the second part of the study are reported in the accompanying paper.⁵ Because of the combination of uncertain benefits, future risks and intrusive treatment, we decided to include an examination of parental and patient understanding and decision making. This was a unique opportunity to study these issues in a trial which was extensive and in which the existing state of knowledge suggested the issues were finely balanced and both advantages and drawbacks were distant and theoretical. Ensuring the entry process to the trial was robust enough to withstand scientific scrutiny in this part of the research led to further clarification and modification of the recruitment procedure.

The recruitment of patients to the study of both physical and psychological effects required us to address the process of imparting neutral standardised information and assisting with informed decision making, at the interface between research and clinical practice. The studies took place in the special circumstances of a clinician and a family who have a long-standing professional relationship in the care of a child with a life threatening chronic illness.

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Accepted 26 February 1995

Further complexity was added by the need to standardise the recruitment process between the four paediatric centres where the study took place. This highlighted, particularly, issues of communication and informed consent and a series of questions arose about existing practice, for example:

- How precise was the information given to parents about benefits and drawbacks of treatment in each patient group?
- Should information about *all* possible side effects always be included?
- What should the practical procedures be in recruiting patients when the issues in the trial were complicated?
- Whose views (parent and/or child) should properly be taken account of in making the decision about entering the trial?
- In what ways did the existing relationship with the clinician affect the decision about the trial: should the clinician always be neutral in giving information about a clinical trial?

As a result of these questions we modified the recruitment process at the outset.

Recruitment process

INFORMATION SHEETS

Information sheets were already available for the growth hormone trials. We found considerable modification was required to ensure standardisation of information and new information sheets were written. A checklist for the clinician was drawn up to accompany each sheet (see appendix). The following areas were those in which modification was required.

The possible side effects that were anticipated from growth hormone treatment had to be specified. These side effects included deterioration in renal function, increased risk of rejection, hypertension, and hyperglycaemia. The profile of possible side effects varied for each of the treatment groups. The relative risks of the treatment in each group needed to be detailed.

Possible benefits of the treatment trial were described only vaguely, allowing patients to develop unrealistically optimistic (or pessimistic) ideas. We found it necessary to introduce more precise information on benefits.

Experimental design meant that one group of patients had random allocation to either growth hormone or no treatment, whereas the remainder all had growth hormone in the first year of the study. The meaning of 'random allocation' needed spelling out more precisely to avoid confusion about what the consequences of entry to the trial meant.

Although there is a small, unquantified as yet, but recognised risk of malignancy arising during treatment for renal disease, particularly in the transplanted group, this was not mentioned in the information sheets (before or after modification).

PROCEDURES IN RECRUITING PATIENTS

As we realised the complexity of the information to be conveyed and the fine balance of the

decision to enter the trial, it was appreciated that more time than usual was required to introduce the study to patients.

All patients meeting the criteria for the trials were invited to an outpatient appointment outside their normal review. The entry criteria were applied strictly with no pre-exclusions. A specific example illustrates the way in which well meant preconceptions may lead clinicians to bias the sample entering a study, if this procedure is ignored.

C is a 16 year old boy with severe learning difficulties and behavioural problems, whose adoptive mother has severely impaired vision because of diabetic retinopathy. The consultant's initial view was that the trial was inappropriate for this child and his family. Reasons for this included possible difficulties in administering the growth hormone, the child's likely poor response to it and, perhaps, a prejudice that the eventual quality of life of this individual when an adult would be little influenced by the size he achieved. He did, however, fit the criteria for the study and one of the reasons for his having received a predialysis transplant previously was that his growth was extremely poor; at that time his adoptive mother thought that his short stature would have a serious impact on his quality of life in adulthood. The discipline of following the carefully constructed information sheet and systematic planning of the subsequent clinic interview, particularly the use of the checklist, ensured that neutral information was given to the family. Thus the decision about entering the trial was theirs, rather than being prejudged by the clinician. The parents opted for growth hormone treatment with few practical problems and the boy has shown a good initial response to treatment.

First interview

The current status of growth hormone treatment in renal failure was discussed and the questions being addressed by the studies were introduced. Patients wishing to give serious consideration to entering the study were given the modified information sheets and a further interview was arranged.

Second interview

The study and information sheet were discussed in detail.

(A) The clinician had to ensure complete coverage of a nine item checklist (appendix) which listed all important information to be given.

(B) The potential response to growth hormone was made as specific as possible for the individual patient, for example, by demonstrating on a height chart the consequences for the individual patient of a 50% increase, and of a doubling of the height velocity.

(C) Further interviews were offered if more time was required for a decision: the offer was accepted by about 50% of families.

Further interviews

Further interviews were intended to clarify any aspects of information; the checklist and information sheets helped with this. Other functions, however, emerged and it became evident that time was required, on occasion, to facilitate decision making and to ensure that unhelpful and even punitive methods of making the decision had not been adopted.

Facilitating decision making: the 'familiar clinician' effect – The clinicians in this trial had all the usual concerns about the medical issues in the trial. In addition, they knew their patients, and the patients' families, extremely well, often having been involved in providing life saving treatment and having made difficult decisions about dialysis, transplantation, and surgery. In turn, the parents normally rely heavily upon the advice of experts in these situations, and are used to viewing the professionals as sources of advice in an area where they are themselves rather ignorant. The growth hormone trials were quite different. The area of medicine was relatively unfamiliar to the clinicians, and the benefits uncertain. The problem (short stature) was not life threatening and the treatment involved benefits at a psychological level, but with a complicated study design and cost-benefit analysis. Both parents and professionals found themselves in a novel relationship to each other and the decision, with power located differently from its distribution in other aspects of illness and treatment.

Although at the outset, the clinicians in the study deliberately adopted a neutral stance, inevitably, the history of close contact between the parents, their children, and the clinician led to the latter being invited to take part in the decision. The response to this invitation was first to review the information and second to stress that the trial had been properly constructed and was addressing an issue about which there was uncertainty. Despite this, inevitably some families still requested advice and often were unable to make a decision. This resulted in a definite two stage approach for these families: initially, imparting neutral information and subsequently offering help with the decision when real difficulties became apparent. This provides, we consider, the best balance between the need to maintain scientific validity in recruitment to the study and the traditional medical role of advice and guidance.

Monitoring decision making: the 'punish the adolescent' effect – In the course of discussions about entering the trial, aspects of parental thinking came to light, related to this non-life threatening area of treatment. Two patients (age 13 and 16 years) had had unsuccessful treatment with growth hormone in lower dosage previously. It was obvious, in the discussion, that their parents intended to let them take the decision about whether to enter the trial. One can appreciate that their parents thought these children were better informed about the burden, and likely effect of, treatment than were other children entering the study: they could be judged as competent to

choose. In both cases, however, the decision was handed by parents to their child in a punitive way. The teenage sons were told it was their decision and if they opted for treatment, they must not complain about the daily injections. In a third case, a decision to choose growth hormone treatment was made by a 16 year old boy with the apparent support of his parents but after protracted discussion. Subsequently when growth hormone injections had to be stopped because of deterioration in transplant function, the father's comment was that if the parents had had their way, their son would not have received the treatment in the first place. In essence, the father was blaming his son for the physical deterioration which occurred after his entry to the trial.

Prevention of these negative consequences of the study is possible in the subsequent interviews if clinicians are alert to these issues and trained to deal with them.

Understanding and decision making

EVALUATION OF UNDERSTANDING AND DECISION MAKING

Children's and parents' understanding of growth hormone treatment and decision making about participation in the research trials was evaluated during a semistructured research interview shortly after the recruitment interview with the paediatrician. The interview was carried out by independent research workers in separate assessments of parents and children. Both were asked what they knew about the treatment. The knowledge they reported was compared with information from the checklist used by the clinicians and a rating of overall understanding was given by the interviewer. This was on a three point scale (0=poor/limited understanding, 1=good/some misconceptions, 2=very good understanding). To score in the 'very good' category all relevant items on the checklist had to be mentioned spontaneously and a good understanding shown of their implications. Parents and subjects were also asked how they had reached their decision to participate in the trials, and asked to indicate the ease of making this decision on a three point scale (easy, some difficulty, a lot of difficulty about making the decision).

Results

Thirty families took part. Only 14 patients (age range 9–18 years, mean 13 years) were

Interviewers' ratings of parental and child understanding and decision making; figures are number (%)

	Parents (n=30)	Children (n=14)
Understanding of treatment		
Poor/limited	6 (20)	5 (36)
Good/some misconceptions	15 (50)	6 (43)
Very good	9 (30)	3 (21)
Ease of decision making		
No difficulty	21 (70)	2 (21)
Some/minor difficulty	5 (17)	7 (50)
A lot/major difficulty	4 (13)	4 (29)

competent enough to complete all parts of the interview. The table shows the interviewers' ratings of parental and child understanding.

PARENTAL UNDERSTANDING

A great majority (80%) of parents had a good or very good understanding of the treatment trial. Among the six parents whose understanding was poor, ignorance and uncertainty were mainly about side effects and expectations of outcome rather than details of what the treatment involved. English was not the first language of three of these six parents.

CHILDREN'S UNDERSTANDING

Despite the children being older, relatively competent subjects, 36% (5/14) were unable to understand or recall in any detail the information given about the treatment trial. One 14 year old boy said he had not been told anything directly by the doctor and had had minimal information relayed by his mother.

No correlation was found between the level of children's understanding and age (Spearman's rank correlation coefficient=0.333), nor was there a significant association between the level of children's and level of parents' understanding about the trial ($\chi^2=3.4$, $df=3$, $p=0.48$).

EASE OF DECISION MAKING

The table shows that nearly one third (30%) of parents had difficulty deciding whether or not to accept growth hormone treatment. A mixture of information and discussion with the doctor was cited by parents as being of most help in the decision making process. There was no association between the ease of parental decision making and the parents' level of understanding about the trial ($\chi^2=7.51$, $df=4$, $p=0.11$). Of 24 parents with good/very good understanding four reported a lot of difficulty deciding about treatment. None of the six whose understanding was poor said they had a lot of difficulty deciding; two reported having some problems but four said they had no difficulty. There was no association between the ease of parental decision making and the degree of parental concern about the child's growth ($\chi^2=7.9$, $df=8$, $p=0.09$), where concern was rated on a 0-1-2 scale (see J M Reynolds, *et al*⁵). We looked for possible associations between the ease of parental decision making and physical factors in their child. We found no statistical relationship of significance between the ease of parental decision making and child's age (Spearman's rank correlation coefficient=0.132), child's height (Spearman's rank correlation coefficient=0.189) or the type of treatment for renal disease ($\chi^2=5.78$, $df=4$, $p=0.21$).

Children reported more difficulties than parents in deciding about treatment though the difference did not reach statistical significance

(Spearman's rank correlation coefficient=0.272). In discussion during the interview, it was clear that most children felt the final decision about treatment had been made jointly with their parents. Only one subject, an 18 year old youth, described it as his own decision.

Discussion

In these studies, issues arose with regard to recruitment, information giving and the roles of parents, children, and clinicians in decision making. We have found the process of scrutiny of our procedures and information, initiated by the demands of the various studies, provoked much thought about the demands of clinical trials.

Using modified information leaflets and the clinician's checklist, the majority of parents in our sample showed high levels of understanding of illness and treatment issues, suggesting that this system of giving information and explanation about the trials was effective. The fact that English was not the first language for three of the six parents with poor understanding is important and clearly more thought should have been given to providing information which took account of language difficulties.

Despite good understanding, one third reported difficulty making the decision as to whether or not to accept growth hormone treatment. Good understanding neither facilitated nor inhibited decision making; it was neither necessary nor sufficient. Having a thorough understanding of their child's illness and the pros and cons of treatment could either lead to a carefully considered decision being rated as 'easy' or, overwhelmed by evidence, parents may have great difficulty in deciding about the trial. There is an evident need to give good impartial information to all approached for trials, but, parents do not make decisions purely on the basis of information. At least when deciding about one small aspect of treatment for a complex disease, they make a choice which may involve the views of the paediatricians, emotional factors and personal style. It does not depend exclusively on more obvious physical factors of their child's height deficit, age, concern about growth, or risks of the treatment.

When recruiting patients to a study this discordance between understanding and decision making creates a tension between the need to impart neutral information to maintain the scientific validity of the study and to guiding the choice. This tension is heightened where the clinician is working with families who are well known to him or her and the issues are very complex and finely balanced. The balance between a guided choice and impartial informing is best achieved if clinical guidance is separated from information giving and delayed until the final stage of decision making. It is helpful to identify a number of stages in this process. First the entry criteria must be applied with no exclusions. Failure to

do this will bias recruitment to the study, as a group of patients is recruited whom the clinicians have already selected as those who will benefit. Failure to approach all patients also compromises the patient's right to information and involvement in decision making. Second, neutral information should be imparted. Checklists are helpful in ensuring that consistent and comprehensive information has been conveyed and also to prevent the interviews being dominated by one or two issues dictated by the clinician and family. At subsequent interviews, the checklist also helps the clinician clarify the point reached in the recruitment process and where the difficulty has arisen; has the family not grasped the information, or is there a real problem in making a decision? The third stage of this process is if the family is clearly unable to make a decision despite adequate information; the clinician may then give advice about the decision, taking into account knowledge of the patient and the family. An independent recruiter to the trials would have been an alternative. This approach would not be without its problems, including expense.

The extent to which children should be involved in decision making is a difficult issue.⁶ Weithorn and Campbell found that 9 year olds were able to express choice and sensible treatment preferences,⁷ but this must be dependent upon the complexity of the issues involved. In the present study, relative costs and benefits were quite hard to evaluate. Korsch suggests that involvement in decision making may help children to undergo research experiences with less anxiety and ambivalence.⁸ The law relating to children has never been clearly established. The application of general principles indicates that, where children have sufficient understanding and intelligence to understand what is proposed, it is they and not their parents whose consent is required by law.² Should the children be allowed to make a contribution to the decision, if it is felt they are unlikely to be able to tease out the complex issues concerned? Most children in our study reported that they had taken some part in the decision making along with their parents. Our findings highlight the need to provide information which is appropriate to the child's developmental level and the extent of their anticipated involvement in the decision.

Our experience with most decisions about treatment for CRF is that parents tend to reserve decision making to themselves, so we were surprised how much the parents allowed the children to contribute. This may occur because short stature is not seen as a life threatening aspect of the illness, unlike other decisions these parents make. Professionals need to be alert to those circumstances where parents faced with a complex decision, involving daily injections and theoretical future risks, may delegate inappropriately and even coerce their children by adopting punitive attitudes.

Finally, raising the issue of growth hormone treatment for our patients and their

families as part of a research study highlighted one of the most important ethical and practical difficulties in conducting treatment trials: the nature of informed consent. Every patient has the right to be treated in the best possible way for his or her condition and to be as well informed as he or she wishes about the possible risks and benefits of any treatment option. We were well aware that despite the rigorous procedures instituted as part of these trials, the small but recognised risk of malignancy arising during treatment was not mentioned in the information leaflets, before or after modification. Currently malignancies account for 7% of deaths after renal transplantation in children.⁹ This is likely to increase with more intensive immunosuppressive regimens. There are theoretical possibilities that growth hormone could increase this risk. We felt on reflection that we were protecting parents and families from this knowledge. How serious or likely should a risk be before it is mentioned in clinical trials? This judgment is made more complicated by the fact that, for some families at least, the increase in information makes the decision more difficult.

Many of the issues raised by this study are of general importance in designing studies. Even when a clinical trial is introduced the information may not be rigorous enough for either proper clinical practice or for research. Consideration of culturally and developmentally appropriate information and checklists should not be controversial. It is helpful to distinguish issues of informed consent to a clinical trial from informed consent for other treatments. For these reasons the recruitment process to this study was very time consuming and this needs to be considered in the planning and funding of studies. We hope that our experiences with this group of children with chronic illness and multiple problems may prompt discussion and consideration of these issues when treatment trials are planned in a paediatric setting.

We would like to thank the parents and children who took part in this study, which would not have been possible without the generous financial support of Kabi Pharmacia. We are also very grateful to the following people without whose help and collaboration the study would not have been possible: Sister J Willock (RMCH), Dr D Milford, Dr C Winkley, Mrs C Hawkins (Birmingham), Dr L Rees, Dr H Maxwell, Mrs S Madden, Sister R O'Sullivan (Royal Free Hospital), Dr T Brocklebank, Sister C Pendlebury (Leeds).

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Appendix

GROWTH HORMONE STUDIES CHECKLIST (of information given to parents during initial visit)

1. Trial patient/parent information leaflet given
2. Purpose of trial
 - (a) To measure improvements in growth rate with growth hormone
 - (b) To measure effects on renal function
3. Small possibility of causing deterioration to renal function (NB. Predialysis and transplant study only)
4. Randomised trial – treatment either from year 1 or year 2 (NB. Transplant study only)
5. Treatment involves daily injections
6. If consenting, day admission required for tests to see if suitable
7. Thereafter, will involve tests on day patient basis every six months (Whether starting growth hormone in first or second year) (NB. Predialysis and transplant study only)
8. Treatment can be stopped at any time, if problems arise or at parents' request
9. Possible/expected outcome of growth hormone treatment

Commentary

'Informed consent' first arrived on the American medical scene in 1957 in the context of daily clinical practice when a court concluded that doctors had a duty to disclose the 'facts which are necessary to form the basis of an intelligent consent' by the patient to a proposed treatment.¹ In the 1960s, after the uproar over the documentation of unethical research in both the United States and the United Kingdom, the concept of informed consent was extended to research. A formal process of obtaining consent from the patient subjects (or parents) and authorisation by a research ethics committee gradually became standard practice. For 'research', the standard of disclosure is higher than that recognised for 'treatment' simply because of the greater uncertainties involved. Smithells has pointed out the paradox: 'I need permission to give a new drug to half my patients, but not to give it to them all', and warned that this higher standard might have the effect of obstructing high quality research and thus of promoting the use of unproved and possibly harmful treatments in an uncontrolled fashion.² In this paper, no mention is made of any discussions with a research ethics committee, but I assume that this clinical trial was considered as 'therapeutic research' rather than conventional treatment though genetically engineered growth hormone is regularly used in other circumstances.

The trial illustrates some of the frustrations of trying to achieve a balance among competing interests. The painstaking efforts of Postlethwaite and his colleagues in attempting to maintain scientific validity while respecting the need for the informed consent of their patients are commendable. This was a carefully thought out approach to a difficult problem, but it is difficult to avoid the impression that some recruitment bias must have been introduced by the rather complex process of obtaining 'staged' informed consent. At four paediatric centres, treatment was offered 'to all patients who met the entry criteria'. These criteria are not stated, and no information is given on the proportion of refusals, either at the outset or after attempts at increasing patient understanding. Patients had 'random allocation to either growth hormone or no treatment whereas the remainder all had growth hormone in the first year of the study'. This random allocation is difficult to follow.

'Neutral standardised information' was provided 'in the special circumstances of a clinician and a family who have a longstanding professional relationship in the care of a child with life threatening chronic illness', but as the investigators discovered, it proved impossible to remain neutral and 'help with the decision' was given when difficulties became apparent.

In a state of uncertainty about the benefits and risks of treatment and relatively small numbers of patients, a fully randomised control design involving more centres, and perhaps using an independent recruiter, might have avoided some of these difficulties. It would also have provided safeguards: 'the hoped for benefits and unanticipated risks are distributed equitably and there is the potential for reducing the number involved in any therapeutic disaster'.³

In spite of all these efforts, it proved difficult to achieve patient and parent understanding, even in the context of a longstanding therapeutic relationship. They indicate that 'good understanding neither facilitated nor inhibited decision making', yet state that 'overwhelmed by evidence, parents may have great difficulty in deciding, and that 'none of the six whose understanding was poor said they had a lot of difficulty deciding'. Do these responses not simply imply that, for some participants at least, the less understanding there was about the study, the easier it was to decide to enter – a problem of consent that is not unique to this study. In research as in other aspects of the doctor-patient relationship, much still depends on trust!

The validity of informed consent for treatment is usually reviewed only in retrospect at the time of a lawsuit for malpractice. In the context of research it has not been tested to date. After the landmark case of *Sidaway v Bethlem Royal Hospital*,⁴ it seems to be generally accepted, in this country at least, that 'appropriate disclosure' of the risks of a particular treatment should be judged, not by some absolute standard, but by the 'prudent doctor' test, and according to the standard adopted by other careful practitioners. This usually means that the doctor retains some discretion, and does not have to disclose a particular risk to a patient if he considers that to do so would threaten the patient's mental or physical health. For research, even therapeutic research, it is axiomatic that the requirements are more stringent. There will be some who will be critical of the investigators for not disclosing 'a small but unquantified risk of malignancy'. In the circumstances described here, I believe that the judgment of the clinician-investigators was correct.

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