

Practical issues in relation to clinical trials in children in low-income countries: experience from the front line

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ABSTRACT

Clinical trials in children in resource-poor environments are essential for local health policy and practice to be relevant and evidence based. Research must be ethical, appropriate, relevant and of good quality. It should, where possible, benefit the subjects studied, the clinical, scientific and support staff involved, and the service and academic institutions of the host country. The challenge for researchers and their sponsors is to maximise such benefits while avoiding the many possible pitfalls.

INTRODUCTION

Much thought and writing has recently been devoted to the subject of clinical trials in children in low-income countries.^{1–3} The number of clinical trials done in low-income countries is low; from 1996 to 2002, only 22% of randomised controlled trials were from middle- or low-income countries and although most (56%) were in appropriate areas (infections, infestations), very few mentioned the involvement of a data safety management board or a local ethics committee.⁴ In 2009 Standards for Research in Child Health was formed with a mission to improve the design, conduct and reporting of paediatric research.⁵ The WHO, through the Better Medicines for Children programme, is trying to improve access to and quality of medicines for children worldwide and is advocating high quality and ethical research in diseases of children.⁶ The authors of this paper have each participated on the ground in various capacities in such trials over many years. We hope that our reflections on this experience may be of some interest or value to others engaged in this essential activity.

WHY SHOULD THERE BE ANY CLINICAL TRIALS IN CHILDREN IN THIS CONTEXT?

Children in low-income countries are doubly vulnerable—through a combination of immaturity and poverty—and any trial involving them must have stringent ethical justification. The ethical injunction against doing harm must be balanced by the equally compelling ethical imperative of beneficence. In our view, there can be no doubt about the need for clinical trials in this population for many inter-related reasons: (1) disease problems in this group are enormous; (2) the problems differ from those prevailing elsewhere, and therefore are not available for study elsewhere; (3) solutions feasible in other environments are, in any case, commonly not feasible where resources are few; and (4) for many potential interventions, well-conceived and well-conducted trials provide

the best—often the only convincing—evidence of benefit or otherwise.

An example fulfilling all four of these justifications is the programme to demonstrate the value of the pre-referral administration of artesunate by suppository to villagers with life-threatening malaria. (1) Malaria kills about three-quarters of a million people every year; (2) nearly all of these are young children in Africa; (3) the appropriate parenteral therapy is usually not available locally and quickly, as it might be in wealthier communities; (4) there is no adequate surrogate index for life-saving efficacy—only a trial with a mortality endpoint could prove the benefit of suppositories. Preliminary trials proved the principle⁷ and a multicentre international trial demonstrated efficacy against death in children and adults with delayed access to hospital.⁸

Many issues that become problematic during or after a trial could have been prevented or eased by addressing them before the start. Most countries now have research ethics committees, which increasingly ensure these matters are thought about in advance.

WHO CHOOSES WHAT WILL BE STUDIED AND HOW A TRIAL WILL BE DESIGNED?

It has been common for ideas for trials to be generated outside the country or countries in which the trial will be conducted. This is becoming less necessary as academic groups and institutions in low-income countries become stronger. We recognise that many valuable ideas will continue to come from elsewhere and will be welcomed, but at the very least the understanding of the problem, the appropriate intervention and the study design should be developed through a real collaboration involving host country scientists. In-country paediatricians and scientists know the nature of the problem better, know what has been tried before and what can and cannot be done, and will be around afterwards to see through the consequences.

It is particularly difficult to achieve local participation in the preparatory process when a proposed study is part of a multi-centre or multi-country trial, for which a consistent protocol is necessary between sites. It is then common for a generic plan to be developed and delivered fully-formed to each participating country. This may be unavoidable, but the host-country participants must have the opportunity to suggest improvements or modifications and should be fully involved in the analysis, interpretation and dissemination of results.

The protocols for a multicentre vaccine study in infants were prepared in Europe and North America. The local team thought that the consent form was too complicated and long (17 pages). They tried reading it to several mothers in a baby clinic and demonstrated that it was incomprehensible to them. The local team proposed that posters visually depicting the text of the informed consent form would be more informative. They designed twelve posters and a 'feed-back form' with 20 questions covering issues that were most important for the mother to understand before signing the informed consent form. This process achieved a high level of comprehension among mothers.

In the same study, diary cards to be completed by mothers had been designed abroad for participants assumed to be literate. The local team developed illustrated diary cards that were successfully implemented and improved the quality of data capture.⁹

Informed consent

The above example also illustrates the importance of informed consent being real rather than merely fulfilling statutory requirements.¹⁰ A lengthy document may convey less information than a short one, especially if participants are illiterate and the material must be read to them.

Information should be provided to the community and not only to those enrolled in the study

In a trial involving infants, the protocol required taking small volume of blood samples at intervals over a period of months. Mothers consented, but during the trial rumours began to circulate that much larger volumes were being collected and that the blood taken was being sold abroad. The rumours appeared to have originated among older and influential people in the community, and several mothers withdrew from the trial or declined enrolment. The investigators held discussions with village representatives and committees, after which the rumours ceased and the trial proceeded according to plan.

Consulting the community

It is both courteous and necessary to discuss a community-based trial with the wider community well before the plans are finalised. Apart from demonstrating due respect, such openness and communication have practical benefits that may go beyond simply improving compliance by participants in the study. Community members may provide essential insights into what is feasible, what is acceptable and what will promote the successful conduct of the research.

In a neonatal study, babies were to be followed up in their homes during the first seven days of life by a field worker. Consultation with the community established the fact that it was culturally unacceptable for any man except the baby's father to visit a home during the first week of a baby's life. It also became clear that it was unsafe for a woman to walk alone through maize fields to visit homes. The protocol and budget had to be changed to provide only female field workers and for them to work in pairs.

For a clinical trial conducted in hospital, there may not be an accessible community to consult in advance. However, it may be possible to confer with communities around individual patients during the follow-up period. Some hospitals have a committee for liaising with the surrounding community. Hospital staff, many of whom may originate from and/or live in the local community, may also be able to provide a valuable community perspective.

Ancillary benefits, recompense, incentives and coercion

There is no simple formula to calculate how much benefit, apart from the knowledge gained from the research, should accrue to enrollees or to their community as a result of their participation in a trial.¹¹ To expect individuals or communities to comply with the demands of a trial and to provide no assistance at all, or to enter an impoverished community with medications required for a trial but to ignore all other needs, are approaches that are generally agreed to be inhumane and unethical. On the other hand, to offer large benefits contingent upon enrolment in a trial is correctly seen as undue coercion. We believe that the right balance can only be achieved by careful consideration at the level of the community and the local research ethics committee.

In a trial in infants, mothers were required to bring their babies to the study clinic on 17 occasions during the first six months of life. In preparatory discussions with the community, the investigators learned that a mother considers it important that both she and her baby should be clean and presentable when attending a clinic. Few mothers could afford the soap needed to achieve this. The investigators therefore proposed that each mother should receive a bar of soap for the period of involvement in the study. The sponsors refused to allow this compensation to be given to mothers arguing that it constituted 'undue coercion'. They were impervious to discussion on this issue, and mothers had to find their own soap or leave the trial.

On an issue of this kind, sponsors based at a distance and in societies remote from the scene of the trial should not, in our view, impose their requirements without very careful consideration of the experience and judgment of those living and working on the ground where the trial is to be conducted. In the example quoted, the sponsors' refusal to allow a bar of soap to be given to mothers imposed hardships on trial participants and threatened the cordiality of the trial and the success of long-term follow-up.

The two latter principles—of consulting the community and providing appropriate compensation or ancillary care (without undue coercion)—may conflict.

At the end of a vaccine trial involving children, the investigators met with the participants to discuss continuing support for facilities at the local health centre. The investigators intended that the ongoing assistance should be available to the whole community, whether involved in the trial or not. The participating families objected that it was unfair for those who had not gone through the trouble of enrolling their children in the trial to receive as much benefit as those who had.

It remains important that undue coercion should not be applied with the aim of achieving a research objective. In general, it is the local ethics committee that recognises potential coercion and proscribes it.

In a cancer study in which a fine needle aspiration sample was taken for diagnosis, a research team proposed paying for extra samples to be taken for research. The amount to be paid was more than what a manual worker receives for a day's work. This was seen locally as coercion and the researchers were asked by the national research ethics committee to remove this payment and instead assist with funding follow-up and inpatient supplementary feeds.

Knowing and linking with the local academic community

Whether a trial is part of an international multi-centre study or is entirely local, great care must be taken to establish what

kind of similar work has already been undertaken in the vicinity, who has conducted it, and which individuals, groups or institutions should be consulted and invited to participate, or at least informed before the plans are laid. In general, several parties have a stake or an interest in a problem area. They may have valuable—possibly essential—inputs to provide, that will help the study to succeed, but if they feel ignored or bypassed, their resentment could be obstructive.

A study was designed from within an international research institute with funding from a research agency. For the study to be approved by the local ethics committee, a covering letter was required from the hospital department in which children were to be enrolled. It was only at this stage and because of the need for a supporting letter that the department became aware of the study. This failure to consult, inform and involve the hosting facility in advance of seeking ethical approval caused anger and delay. The resulting friction between the hosting department and the research institute was only rectified by lengthy diplomacy and negotiation. Early and open discussion and mutual involvement in the design and/or conduct of the study would have contributed to a speedier, more efficient and more cordial research activity.

Relationship with local clinical service providers

Many clinical trials must identify and enrol patients from within a health facility. Relationships between the trial staff and the local service staff then require careful consideration. To be conducted successfully, the trial needs adequate staff, equipment and drugs, while the host facility may have serious shortages of all these. Such disparities may be a source of conflict and resentment, but they can also be turned to mutual benefit of both teams.

A trial of a new antimalarial drug regimen required enrolment of children with severe malaria admitted to a large hospital. In order to identify cases, blood samples had to be taken promptly at the point of entry to the hospital from all very sick children, to identify parasitaemia, to measure haemoglobin and glucose concentrations and to culture blood for bacterial pathogens. Since these tests were required from many more children than those eventually fulfilling the trial enrolment criteria, the study provided an expanded and dependable diagnostic service for the hospital. The triallists included clinicians who devoted a proportion of their time to service delivery, through which they both enhanced the strength of the service and benefited from the opportunity to maintain clinical experience and to identify cases for the trial.⁷

A research team is likely to be better resourced than the local clinical service, and there may be disparities in staff salaries and in the apparent workload demanded of team members.

A trial in neonates required the enrolment of women at parturition and the collection of blood samples from the newborn and from the placenta. Midwives were employed to enrol the mothers and to collect the samples. The labour ward was understaffed, and it became a source of resentment that the trial midwives appeared to be under-occupied for long periods of time, while service staff of the unit struggled to cope with an excessive workload. Eventually a scheme was developed by which both the service delivery and the research activities were shared between the two groups of staff, with a modest supplementary remuneration paid to the service staff for their contribution to the trial. The study was then completed cordially and efficiently.

Box 1 Underlying principles

1. Good quality, relevant, ethically sound clinical trials are needed in low-income countries.
2. Close collaboration with local researchers and clinicians from inception to completion of the study is ideal.
3. Sensitivity to and awareness of the interaction with local health services and the community are essential.
4. Feedback to the community is important and much appreciated.

Capacity building and training

The best way to learn how to conceive, design, plan and conduct a clinical trial is to be involved in doing it. The trial itself is therefore an opportunity for training in the skills required of a triallist. In addition, there may be specific ways in which a trial can be the occasion for formal training of some staff to diploma, masters or doctoral level.

An international donor funded a clinical trial in a country with very limited resources. All data were stored and analysed abroad, and were not available to the national disease-control programmes for analysis; no capacity for data storage, management or analysis was built within the host country.

By contrast, in two large multi-centre and multi-country trials, on-site clinicians received training in the triage, assessment and diagnosis of children with severe disease—in one study for the purpose of enrolment to the trial, in the other for the identification of end-points. The health facilities were strengthened with equipment and reagents that were available for all patients. Methods of data collection and protection were installed. Several clinicians and scientists were funded for Masters or PhD programmes.^{12 13}

The changing epidemiology of disease

The incidence and pattern of many diseases, especially infections, vary over time as a result of climate changes, population movements or control programmes. This may affect the achievement of an intended sample size for a clinical trial.

A randomised trial of alternative therapies for acute bacterial meningitis in children was designed and funded on the basis of the incidence of the disease over the preceding few years. After the trial had been approved and started, the introduction of antiretroviral therapy and prophylactic cotrimoxazole for children with HIV infection or exposure halved the incidence of bacterial meningitis. The introduction of the pneumococcal vaccine reduced the numbers even further. While highly beneficial, these developments made it difficult to enrol the anticipated number of meningitis cases in the study.

After the trial is over

This important aspect is not the subject of this paper, but it requires equally careful attention. Mechanisms must be in place for findings to inform the development of national policies and guidelines; to this end, it can help to involve policy-makers in the design and conduct of a study from an early point. Feeding the results back to a community is appreciated by the community but is a complex process requiring extensive preparation.¹⁴ How ongoing ancillary benefits should accrue to a community after the study, and who should benefit and for how long, also needs special consideration from before the start and after the end of any trial.

CONCLUSIONS

Key points in relation to the conduct of these trials are summarised in box 1. Clinical trials in children in resource-poor environments may benefit not only the subjects studied, but also the clinical, scientific and support staff involved and the service and academic institutions of the host country. The challenge for researchers and their sponsors is to maximise such benefits while avoiding the many possible pitfalls.

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