Research

A major new initiative to improve treatment for children

R L Smyth, A D Edwards

UK Medicines for Children Research Network

The randomised controlled trial is the primary research tool for assessing and developing medical therapies, and undertaking high quality trials must be a central activity for any modern health system. Richard Peto has presented compelling arguments for large simple randomised controlled trials (RCTs) as the main way to control bias and random error, and points out that carefully combining large size and simplicity of design is a highly successful strategy for detecting moderate benefits from treatments.[1]

Within paediatrics there are challenges to this simple and appealing approach.[2 3] For example, in chronic illnesses, the burden of disease in children is usually disproportionately small compared with adults; diagnostic criteria may be less precise and more difficult to apply; and clinical outcomes, used routinely in clinical trials in adults, may be either impossible for children to perform or lack an age specific measure (such as quality of life). At a local level, there are many barriers to recruitment to multicentre clinical trials. A recent study evaluated the attitudes and beliefs held by paediatricians about clinical trials and made a number of interesting observations.[4] Firstly, the perception of many paediatricians was that, in many instances, the risks to children of participating in a clinical trial outweighed the gains. Paediatricians' personal treatment preferences were seen as a hindrance to support for a clinical trial and clearly many paediatricians are often not truly in equipoise around the research question being addressed by the clinical trial. In general, paediatricians with previous research experience were most knowledgeable about RCTs and perceived greatest gains from the participation of their patients in clinical trials. However, even clinicians wishing to be involved in trials will admit that there has been, until recently, a lack of infrastructure to support clinical trials.

Whatever the reasons, it is well recognised that fewer large, high quality, clinical trials are performed in children than in adults. A review of RCTs published over 15 years in this journal identified only 249, of which 43% were funded by pharmaceutical companies.[5] The numbers of children who participated in these trials were generally very small (about half recruited less than 40), indicating that they were unlikely to detect moderate differences in treatment effects. Where the research base of paediatric subspecialty areas such as cystic fibrosis,[6] rheumatology,[7] and community paediatrics[8] have been reviewed, the findings have been similar. There is now growing awareness that this is not merely an academic problem, but one which has direct consequences for the care of children.

A large proportion of drugs used in the treatment of children are unlicensed or off label. In the UK, in paediatric patients, 25% of prescriptions fall into this category,[9] and in centres across Europe this proportion is 46%.[10] Many recently marketed medicines do not have licences or authorisations that include children. Of the 45 new substances licensed in Europe between 1995 and 1998, 29 could be used in children, but only 10 were actually licensed for use in this age group.[11] Under these circumstances it is difficult to agree that research with children carries more risk than carrying on using untested or inappropriately formulated therapies.

Despite these obstacles, there are some notable sub-specialties in paediatrics where there is a good track record in performing clinical trials. These include paediatric oncology, neonatology, and, more recently, HIV. The United Kingdom Children's Cancer Study Group runs a range of phase I, II, and III trials in all areas of childhood cancer, except leukaemia, and has extensive collaborations in international clinical trials. The National Perinatal Epidemiology Unit in Oxford includes a clinical trials unit which has coordinated many of the multicentre clinical trials with newborn infants in the United Kingdom, over the last two decades. These have included a number of large and complex clinical trials. In trials of therapies for HIV, collaborative groups have had to overcome great obstacles such as considerable stigma, cultural and language barriers, and issues around parental consent and children's assent.[12] These three examples are notable in that clinicians have all developed and run their clinical trials through clinical trials units, where core staff can provide expertise in statistics, trial management, and information technology. This expertise is essential to ensure high quality, successful, and timely conduct of clinical trials and to meet regulatory and governance requirements.

In other specialties there are new initiatives for collaborative research and indications that the situation may be starting to improve. The British Society for Paediatric Endocrinology and Diabetes has established a Clinical Trials Group which is coordinating multicentre trials of therapy for infants born small for gestational age and for Turner syndrome. The Clinical Trials Unit in Cambridge has been involved in collecting 9500 DNA samples from children with diabetes for study of the genetics of diabetes and its complications, and is currently also coordinating NIRTURE, a multinational, multicentre study of insulin therapy in the newborn. A recent study has compared RCTs published in cystic fibrosis over a five year period from the beginning of 1998 with all the randomised trials identified previously published since 1961.[13] In the recent five year epoch the number of RCTs was approximately half that of the previous 37 years, and 25% of them were multicentre compared to 11% previously. This suggests that there is now some recognition by clinical trialists that to obtain an adequate sample size their study needs to include more than one centre.

Conducting large, simple trials with children is possible. Ten years ago, an important clinical trial compared the safety of paracetamol with ibuprofen for the treatment of fever in children.[14] It recruited over 84 000 children and helped to dispel some of the myths about possible adverse consequences of use of ibuprofen in children. It represents the largest single source of information about the safety of medicines to control fever in children and is relevant to the health of every child. Much can be learnt from its pragmatic design. However, although there are many simple strategies that can be used to enhance the engagement of clinicians in a clinical study, the biggest challenge to improving participation in multicentre trials is likely to be the culture change needed to build up a body of

paediatricians experienced in recruiting children to clinical trials, and to provide them with the infrastructure to do this.

An important new Government initiative aims to make a major improvement in the UK's ability and record in high quality clinical trials for children. In August 2004, the Department of Health and the Medicines and Healthcare products Regulatory Agency announced a Paediatric Strategy. One of the three key components of this strategy was the development of a national research network for investigating medicines for children, ahead of European legislation currently being discussed in the European Parliament, which is expected to recommend a European wide network for conducting clinical trials to address the safety and efficacy of drugs for children. In 2004 the Department of Health announced that one of its four new Topic Specific Research Networks would be a Medicines for Children Research Network (MCRN). The key overall purpose of this network is ''to facilitate the conduct of randomised prospective trials and other well designed studies of medicines for children including those for prevention, diagnosis, and treatment''. After a competitive bidding process, a consortium which included the University of Liverpool, Royal Liverpool Children's NHS Trust, Liverpool Women's Hospital NHS Trust, Imperial College London, National Perinatal Epidemiology Unit in Oxford, and the National Children's Bureau was invited to become the coordinating centre for the MCRN and this is now based in Liverpool (http://www.liv.ac.uk/mcrn/).

The first task of the Coordinating Centre was to call for proposals to establish regionally based local research networks within the Medicines for Children's Research Network. These local research networks within the MCRN will receive considerable funding to improve the infrastructure to support the effective and speedy initiation and conduct of multicentre clinical studies addressing medicines for children. The Centre is also overseeing the development of the portfolio of research; this challenging task is being undertaken by a number of multidisciplinary Clinical Studies Groups, made up of clinicians, consumers, funding bodies, and others generally focused around a recognised sub-specialty. The work of these groups will include developing a priority list of studies to be conducted through the MCRN, supporting investigators in the development of proposals, and obtaining appropriate funding. The MCRN Coordinating Centre is working within the broad umbrella of the United Kingdom Clinical Research Network to develop, for the network, an appropriate training programme, sophisticated information systems, and processes to operate efficiently within the regulatory framework.

All of this work is underpinned by the determination to put children at the heart of the agenda. The National Children's Bureau has considerable experience in working with children to ensure that their views are heard. The UK MCRN will ensure that children and parents are involved at every point in the research process from identifying the questions, developing and designing the studies, overseeing the conduct of the studies, interpreting their results, and disseminating them widely.

Children's research has now been given a high priority. After many years of championing this cause, those involved in the health of children in the UK have finally got resources to set up meaningful infrastructure. The MCRN should be able to deliver high quality clinical trials, to aid investigators in achieving their goals, and to improve the therapeutic landscape for children and infants. This is the greatest opportunity that UK paediatric research has had in the last two decades. The challenge now is to make it work. It is up to us, as UK paediatricians, to pick up the baton and run the race.

Arch Dis Child 2006;**91**:212–213.
doi: 10.1136/adc.2005.077073

Authors' affiliations
R L Smyth, Division of Child Health, School of Reproductive and Developmental Medicine, University of Liverpool, Alder Hey Children's Hospital, Liverpool, UK
A D Edwards, Division of Clinical Sciences and MRC Clinical Sciences Centre, Faculty of Medicine, Imperial College London, Hammersmith Hosptial, London, UK

Correspondence to: Prof. R L Smyth, Brough Professor of Paediatric Medicine, Division of Child Health, School of Reproductive and Developmental Medicine, University of Liverpool, Alder Hey Children's Hospital, Liverpool L12 2AP, UK; r.l.smyth@liv.ac.uk

Competing interests: none declared

REFERENCES

1 **Peto R**, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol* 1995;**48**:23–40.
2 **Smyth RL**, Weindling AM. Research in children: ethical and scientific aspects. *Lancet* 1999;**354**(suppl 2):SII21–4.
3 **Smyth RL**. Research with children. Paediatric practice needs better evidence—gained in collaboration with parents and children. *BMJ* 2001;**322**:1377–8.
4 **Caldwell PH**, Butow PN, Craig JC. Pediatricians' attitudes toward randomized controlled trials involving children. *J Pediatr* 2002;**141**:798–803.
5 **Campbell H**, Surry S, Royle E. A review of randomised controlled trials published in *Archives of Disease in Childhood* from 1982–1996. *Arch Dis Child* 1997;**79**:192–7.
6 **Cheng K**, Smyth RL, Motley J, *et al*. Randomized controlled trials in cystic fibrosis (1966–1997) categorized by time, design, and intervention. *Pediatr Pulmonol* 2000;**29**:1–7.
7 **Feldman B**, Giannini E. Where's the evidence? Putting the clinical science into pediatric rheumatology. *J Rheumatol* 1996;**23**:1502–4.
8 **Polnay L**. Research in community child health. *Arch Dis Child* 1989;**64**:981–3.
9 **Turner S**, Longworth A, Nunn A, *et al*. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 1998;**316**:343–5.
10 **Conroy S**, Choonara I, Impicciatore P, *et al*. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* 2000;**320**:79–82.
11 **Impicciatore P**, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. *Br J Clin Pharmacol* 1999;**48**:15–18.
12 **Menson EN**, Walker AS, Gibb DM. Clinical trials in children. *Lancet* 2004;**364**:2176–7.
13 **Briggs TA**, Bryant M, Smyth RL. Controlled trials in cystic fibrosis—are we doing better? *Journal of Cystic Fibrosis*. In Press.
14 **Lesko SM**, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 1995;**273**:929–33.