Clinical research

Making a difference: the clinical research programme for children

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High quality paediatric clinical research will ensure that tomorrow's children receive new and better treatments

All of us involved in the clinical care of children have a duty to improve that care and one way of achieving this is through research. Attention has rightly been drawn to the lack of clinical trials which have addressed issues of relevance to children's health.[1] There are some demoralising statistics to support these arguments. For example, a review of clinical trials published in this journal over 15 years found that a high proportion had important methodological flaws and in around half the sample size was less than 40.[2] There are similar findings in paediatric specialities,[3] and in community paediatrics only 40% of decisions were supported by research evidence.[4] Yet we are all aware of the dramatic impact which the results of clinical trials have had on the care and survival of children with malignant disease and those born preterm. To illustrate the impact of high quality research on children's health worldwide, I have tried to identify some of the most important clinical trials which have benefited children.

SOME KEY TRIALS

It is tempting, when addressing such a topic, to consider the most important trials within one's own practice, but I tried to provide a more objective assessment, of broad relevance to paediatricians, by using the number of citations of the study report as an approximate measure of the impact of the trial. All measures of ''impact'' are subject to limitations, and papers describing clinical trials may be widely cited for reasons other than their importance to clinical care, for example if their findings are controversial, they address a topical disease area, or they were published a long time ago. So, aware of these limitations, but in the absence of a better measure of study impact, I searched the ISI Web of Science using terms to identify studies with children (with terms including ''child'', ''infant'', etc) connected with the ''AND'' connector with search terms for clinical trials. I sorted the results of this search according to the number of times each paper had been cited, to find the top 10 cited clinical trials with children as participants. The top 10 clinical trials, all of which had been cited at least 300 times, are listed in table 1.

A number of features of the trials included in this list were informative and some were surprising. Firstly, most of these trials have had a major impact on practice. The heptavalent pneumococcal vaccine showed 97.4% efficacy in preventing invasive pneumococcal disease in recipients[5] and this vaccine has now become part of the schedule in the USA, UK and other European countries. This has led to a dramatic reduction in invasive pneumococcal disease in children under 5 years of age.[15 16] The impact of this vaccine has extended beyond the direct benefits to those vaccinated to reductions in this disease in children and adults too old to be vaccinated[15] and in infants too young to be vaccinated,[17] and to a decline in isolates of penicillin-resistant pneumococci.[16] In short, the benefits for public health have been immense.

The second observation is that these trials have addressed questions which can only be answered by studies with children. Too often in paediatric practice, where an illness occurs at all ages, studies are conducted only with adults. This makes two assumptions: firstly, that there is no interaction between age and the disease (the features of a disease or disorder such as asthma or gastro-oesophageal reflux may be different in children compared with adults) and secondly, that there is no interaction between age and the response to therapy. However the trials in table 1 address quintessentially paediatric disorders, such as Kawasaki disease,[8] attention deficit and hyperactivity disorder,[6] respiratory syncytial virus bronchiolitis,[11] etc, with questions which could not be answered by adult studies.

Table 1 includes single centre studies which have originated in the commitment of two investigators to answer an important clinical question (as in vitamin A for severe measles[14]) and large multicentre studies recruiting tens of thousands of children. Non-pharmacological interventions feature prominently, but there is also good evidence of collaboration with the pharmaceutical industry. One aspect which should concern and challenge readers of this article is that none of these trials were led from the UK.

RESEARCH INITIATIVES IN THE UK AND THE MCRN

There is now widespread recognition that, although the UK has an excellent record in biomedical research, it has never realised the potential of one national health service to provide the infrastructure for multicentre clinical research studies. However, all that is set to change with the initiatives announced in the Department of Health (England)'s new research strategy Best Research For Best Health[18] and the formation of the UK Clinical Research Network (UKCRN). In 2004, the Department of Health announced a major investment into new topic-specific research networks, which included the Medicines for Children Research Network (MCRN) (http://mcrn.org.uk/). This network is coordinated by a consortium of university, NHS and charitable organisations, with a coordinating centre based in Liverpool, UK. In England, the majority of the funding will be spent in providing research infrastructure support in six regionally based local research networks (LRNs), which between them cover over half of the population of England. The objective of each LRN is to lead, support and promote research into medicines for children in NHS sites within their geographical area. Each LRN is led by a management team with one or more directors, a manager and administrative staff and is overseen by an advisory board which consists of clinical and academic collaborators, including those involved in primary, secondary and tertiary care of children. While the MCRN requires that all research costs of each study within the portfolio are fully funded, the infrastructure provides practical assistance to researchers, such as support in applying for local R&D and research ethical committee approval, contracts and financing, and publicity for a study (to engage the interest of clinicians, children and families). Most importantly, research support staff (from nursing and other health disciplines) support the identification of participants and their recruitment, from all study sites in the LRN, into MCRN portfolio studies. This will ensure that recruitment targets are met and extension grants to funding bodies to complete recruitment are not necessary.

While the funding for infrastructure support, described above, applies to England, each of the devolved administrations within the UK have developed their own structures for supporting research on medicines for children, thus enabling UK-wide adoption of studies.

MCRN RESEARCH PORTFOLIO

The development of the MCRN's research portfolio is the primary responsibility of MCRN clinical studies groups (CSGs). There are currently 10 of these groups (table 2), which between them cover all paediatric subspecialities. They are each chaired by distinguished research leaders and have a multidisciplinary membership, including research nurses, allied health professionals, consumers, and representatives from the pharmaceutical industry and funding bodies. The roles of CSGs are both proactive (identification of research priorities, development of proposals) and reactive (specialist and methodological advice to investigators, commenting on proposals for the MCRN study adoption committee). CSGs have limited funding support. The MCRN supports a CSG administrator and there are travel expenses for meetings and teleconferences. It is hoped that each CSG will develop close links with relevant funding bodies, which will be mutually beneficial. For example, funding bodies may wish to consider the research priorities identified by CSGs when developing their research strategies. There is already evidence that public funding bodies are increasingly supporting studies of relevance to medicines for children. Recently, the NHS Health Technology Assessment Programme (http://www.hta.ac.uk/) ran an open call for proposals for medicines for children, which has funded eight studies (six trials), which will run through the MCRN. At the time of writing, there are 31 studies (27 trials) in the MCRN's portfolio, with many others soon to be considered.

Table 2 MCRN clinical studies groups

Anaesthesia, Intensive Care and Pain Control and Cardiology
Diabetes, Endocrinology and Metabolic Medicine
Gastroenterology, Hepatology and Nutrition
General Paediatrics
Methodology
Neonatal
Neurosciences
Pharmacy and Pharmacology
Respiratory and Cystic Fibrosis
Rheumatology, Allergy, Nephrology, Infection and Immunity (RANII)
Children's Cancer and Leukaemia Group*

*This is affiliated to the MCRN as a CSG, while recognising that it is also a specialist research network within the National Cancer Research Network.

COLLABORATION WITH THE PHARMACEUTICAL INDUSTRY

One of the aims of the new research strategy is to increase investment by the pharmaceutical industry in clinical research in the NHS. The EU Regulation on Paediatric Medicines, which became law on 26 January 2007, establishes a legislative framework to increase the availability of medicines specifically adapted and licensed for use with children, which have been evaluated by high quality research studies. This will be achieved by a system of requirements and incentives. Companies who wish to obtain a marketing authorisation for a new product which has a potential use in children, will be required to conduct a programme of studies involving children according to a paediatric investigation plan, agreed in advance with the Paediatric Committee of the European Medicines Evaluation Agency. This will be rewarded by a 6-month extension of the supplementary protection certificate (effectively a 6-month patent extension), provided that certain criteria are fulfilled. There is provision, within the legislation, for a European paediatric clinical trials network and an expectation that this network will be needed to support the greatly increased number of studies to assess the efficacy and safety of drugs for children. The MCRN was established before the EU regulation came into force and will provide an efficient and well-organised research framework for the conduct of studies funded by the pharmaceutical industry. The benefits to the industry of running studies through a network include a rapid, single point of access to the infrastructure, prompt and reliable assessment of study feasibility, standardised agreements and transparent costing models, access to clinical research expertise, and the assurance that research will conducted rigorously, efficiently and according to good clinical practice. The provisions within the European regulation will radically improve the amount and quality of information available about the use of drugs for children. The MCRN provides the framework to enable many of these studies to be conducted to a high standard in the UK.

Table 1 Top 10 clinical trials in children

Heptavalent pneumococcal vaccine. *Pediatr Infect Dis J* 2000[5]
Treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999[6]
Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001[7]
A single intravenous-infusion of gamma-globulin compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991[8]
Fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 1997[9]
Reducing children's television viewing to prevent obesity. *JAMA* 1999[10]
Palivizumab, a humanised respiratory syncytial virus monoclonal antibody, reduces hospitalisation from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998[11]
Feeding of bifidobacterium and streptococcus-thermophilus to infants for prevention of diarrhoea and shedding of rotavirus. *Lancet* 1994[12]
Outcomes of a field trial to improve children's dietary patterns and physical activity (CATCH Trial). *JAMA* 1996[13]
Vitamin A in children with severe measles. *N Engl J Med* 1990[14]

MCRN WORKSTREAMS

The MCRN coordinating centre is responsible for a number of other workstreams which support this agenda. We have ensured that the views and perspectives of children and families are central to all elements of the research process. A children and young person's panel (known as "STAND UP, SPEAK OUT!") and parents are represented on many of the key committees within LRNs and the coordinating centre. Children and families will provide input to the prioritisation, design, conduct, interpretation and dissemination of the results of all studies run through the network. Training and education of staff involved in the MCRN is necessary to ensure high standards of research governance and to ensure that individuals feel confident to participate in all aspects of the research process. This is freely provided to all staff by generic courses run through UKCRN, as well as courses addressing issues specific to children's research. The MCRN encourages all investigators who are planning to conduct a clinical trial through the network to do so in collaboration with a clinical trials unit (CTU). A number of CTUs throughout the UK are involved in MCRN studies. The involvement of generic CTUs in MCRN trials is welcomed, as it will lead to more widespread development of expertise in trials with children. For neonatal studies, the National Perinatal Epidemiology Unit in Oxford (http://www.npeu.ox.ac.uk/) includes a CTU with particular expertise in clinical trials with newborn infants and there is a dedicated MCRN CTU in

Liverpool. Finally, UKCRN is developing an experimental medicine workstream which will include early phase clinical studies and studies investigating disease mechanisms. The MCRN is working to ensure that its portfolio includes such studies, which are relevant to children, whilst also addressing the specific issues for children, such as the need to utilise methodologies which minimise invasive investigations.

COMPREHENSIVE RESEARCH NETWORKS

The UKCRN national coordinating centre is setting up a comprehensive research network (CRN) throughout England on behalf of the Department of Health. This will extend the provision of research infrastructure within the NHS to all areas of disease and clinical need and in the future all NHS service support costs for UKCRN (including MCRN) portfolio studies will be allocated through this route. The comprehensive research network will also have responsibility for a number of generic research management functions within the NHS in England for studies supported by the networks, including a central sign-off system to streamline the approvals process and reduce duplication, and provision of ''research passports'' (to enable staff to be involved in research studies in more than one NHS Trust). The MCRN will work closely with the comprehensive research network to ensure that these generic processes are implemented smoothly and fairly for MCRN studies and also to ensure that investigators involved in MCRN studies who are not part of an MCRN LRN are able to fully participate. It is anticipated that service support costs will include allocation of research programmed activities for consultants who are, for example, active in recruiting patients to MCRN studies. This will be an important incentive to enable hard-pressed paediatricians to become fully engaged in the network.

CONCLUSION

The implementation of the MCRN and all other developments within Best Research for Best Health has been rapid. While this is very welcome, the pace of change is such that documents, websites, bulletins and other communications need to be regularly updated. For the MCRN, the implementation of the European regulation has added another changing dimension. The clinical environment also needs to change, to become more receptive to and supportive of clinical research and this will happen more slowly. However, there is now an energy and dynamism which is both exciting and invigorating for paediatric clinical research. The real goal is to produce high quality research findings so that tomorrow's children receive new and better treatments and clinicians have real evidence on which to base their decisions. That is something that we can all sign up to.

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