Clinical trials and children's *medicines*

THE BACKGROUND

Every day, millions of children are prescribed medicines safely and effectively. However, some medicines needed by doctors for their young patients do not have a licence for use in children because, for complex ethical and practical reasons, paediatric clinical trials have not been conducted.

Doctors can, on their own responsibility, prescribe medicines for an unlicensed use. Long experience of prescribed medicines used in this way has, over many years, provided an accepted basis for clinical practice.

But while the system has worked reasonably well, it is far from ideal. Over time, the need to conduct clinical trials in children has become widely accepted, and ways to overcome the considerable difficulties involved are now under careful consideration.

The UK pharmaceutical industry has been at the forefront of discussions as to how this can best be achieved in an ethical way for the benefit of all children who need medicines not specifically designed for them.

THE LICENSING OF MEDICINES

The process that leads to a new medicine becoming available for doctors to prescribe is long, usually taking 10 – 12 years. If the research indicates the medicine is effective and safe, the UK regulatory agency (MHRA) or the EU wide agency (EMEA) will recommend that the medicine be granted a licence for use in the treatment of specific conditions, often for adults only.

The unlicensed or off-label use of medicines in children is significant, including:

- more than 90 per cent of medicines used in neonatal intensive care;
- 45 per cent of medicines used in general paediatric hospital wards;
- 10-20 per cent of medicines prescribed for children in general practice.

In addition, licensed medicines are often used in an unlicensed way, e.g. crushed in drinks, which could affect absorption.

PRESCRIBING FOR CHILDREN

There are practical challenges in prescribing medicines for children. Some body systems are not yet fully developed, as in babies, and metabolism varies. For instance, an eight year old may have a faster metabolism and therefore sometimes may need a higher dose of a medicine relative to bodyweight than would an adult. In fact, international guidelines on paediatric clinical trials have divided children into five distinct age groups.

Many medicines have been used off-label in children for years and appropriate dose levels for them are well established. But this is not uniformly the case and establishing best practice is not easy. Articles in journals or talks at professional meetings, for instance, filter through unevenly to prescribing physicians.

Communication difficulties inherent in off-label use may mean that new knowledge takes longer to gain acceptance. This may be further complicated by the likelihood that, given the professional liability they can potentially incur when using a medicine off-label, doctors may not always report side-effects as readily as they otherwise would.

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WHY ARE CLINICAL TRIALS NOT CARRIED OUT ON CHILDREN'S MEDICINES?

In the past, many people and some consumer groups have had strong objections to conducting clinical trials in children. Some people feel that children, who are dependant on others to make appropriate decisions on their behalf, are too vulnerable. Some say that parents of ill children may not be in a state of mind to make informed decisions and should not be put in that position. Other people just think it is wrong, in any circumstances.

There are also practical difficulties in setting up paediatric trials. Locating the number of children in each age group fitting the specific criteria necessary for statistically meaningful trials takes time. This is particularly so as parents – even those who fully accept the importance of such trials – may be reluctant to consent to their child participating.

But in the absence of formal clinical trials, all young patients given medicines that are not licensed for them become, in effect, part of an unofficial clinical trial, with no:

- agreed protocols;
- ethical committee approval;
- formal mechanisms to capture the data;
- efficient channels through which to disperse the information.

WHAT CAN BE DONE?

Proposed EU legislation will require paediatric clinical trials for medicines likely to be used regularly in children. However, it will be some time before the final EU regulation is approved.

The ABPI has participated in the International Conference on Harmonisation (ICH), made up of the medicines regulatory bodies and the pharmaceutical industry trade associations of the US, EU and Japan, which has produced international guidelines on the development of medicines for children. This is a major step forward, as it would be unworkable if research had to meet varying requirements in different countries.

The ABPI has encouraged the establishment of research networks and departments in the UK where clinical trials in children can be concentrated so that the necessary expertise can be developed. The ABPI is also sponsoring two of the three current specialist registrar trainee posts in paediatric clinical pharmacology, which should lead to considerable expansion of UK expertise in paediatric clinical trials. The Government has recently announced the development of a UK Paediatric Research Network.

Adverse reactions to medicines used off-label also need to be scrupulously reported by doctors to the MHRA. Information in this area is available from the MHRA and the Drug Safety Research Unit at Southampton.

LEGISLATION

The pharmaceutical industry supports the development of legislation that requires clinical trials in children where appropriate. (Some medicines are not appropriate for use in children, e.g. medicines for Alzheimer's disease.)

The ABPI will be working throughout the EU and UK legislative process to ensure that clinical research in children is conducted:

- in an ethical way;
- with wide professional and consumer support;
- under agreed international guidelines.

It is also crucial that the requirement for clinical trials in children does not lead to delays in the licensing of medicines for use primarily in adults. It would be wrong to deny adults the benefits of new medicines while paediatric trials are carried out.

Clinical research in children is inevitably more expensive than equivalent research in adults. Therefore, adequate incentives need to be in place to encourage such research to provide children with licensed medicines.

US legislation covering paediatric clinical trials recognises this and includes a number of important provisions for cost recovery which need to be examined carefully to assess their impact. It remains to be seen if the proposed EU legislation will include adequate incentives to provide data to support the use of medicines in children, and so increase paediatric research in Europe.

CONCLUSION

ABPI agrees that medicines regularly used to treat children's medical problems should go through formal clinical trials specifically for paediatric use. Without such trials, medicines must be used off-label, on the doctor's own responsibility, and without input from the originating company.

Ethical committees, which oversee all clinical trials in the UK, should recognise that clinical research in children is ethical and appropriate. The conduct of such trials must be carefully thought out to protect the well-being of the young patients involved and proper economic incentives need to be in place to make it realistic for a pharmaceutical company or any other research organisation to undertake them.

It is vital that the complex issues surrounding the licensing of medicines used regularly in children are resolved for the benefit of millions of today's children and for the generations to come.