MEDICINES FOR HEALTH

Current issues in Paediatric Clinical Trials

Meeting Report

The Association of the British Pharmaceutical Industry

The views expressed in *Current issues in Paediatric Clinical Trials* are the opinions of those concerned and do not necessarily represent the views of the ABPI.

Medicines for a healthy future

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Current Issues in Paediatric Clinical Trials

A meeting held at the Royal College of Obstetricians, London on 13 October 2004

Meeting Objectives

There is currently a range of important ethical, medical and regulatory issues concerning clinical trials that are under discussion at national and European levels. While all medicines used to treat children have been rigorously tested before their general use, not all of them have been authorised for use in children. The meeting aimed to explore this complex issue with other stakeholders, to update delegates on important developments and to encourage open and thought-provoking debate.

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Introduction

Dr Richard Barker, Director General, The Association of the British Pharmaceutical Industry

The UK has long been a leading nation in medicines development and clinical research – a record driven by the highest standards of scientific research and the huge investment made by the pharmaceutical industry. Treatments discovered in Britain have helped to save lives, reduce suffering and improve the quality of life for millions of people all over the world. UK companies reinvest more than a third of their UK turnover in research and development.

Three million children in the UK have a long-standing illness or disability. Although all of the medicines used to treat their conditions have been rigorously tested before being granted their marketing authorisation, not all of them have been tested and licensed specifically for use in children.

There are many ethical and practical reasons why this should be so, but it is clear that we need to gain a better understanding of how medicines work in children, whose body systems are not the same as adults'. Nor is the metabolism of a new- born baby the same as a 17 year old's. So trials need to be particularly carefully designed and run if they are to give us the information we need for prescribing to children.

There are plenty of initiatives seeking to address the current state of affairs. The Department of Health is setting up Clinical Research Networks to take a strategic oversight of research efforts across the UK. The pharmaceutical companies who carry out most of the research into the use of medicines for children have to submit their proposals for studies to research ethics committees, who will assess the risks and benefits involved. The European Union has made proposals for a Regulation of Paediatric Clinical Trials which will be adopted in the coming months. Its objective is to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children.

This conference brings together the many strands of this complex subject. The ABPI agrees that medicines which are regularly used to treat children should go through formal clinical trials to determine their use in children. The result should be more licensed medicines and better health for our children.

Why the issue of medicines for children has come up the agenda

Professor Sally Davies, Director of R&D, Department of Health

Professor Sally Davies is the Director of Research and Development for the Department of Health. Her previous roles include Deputy Director of Research and Development for Delivery, Director of R&D for the London DHSC/Region and Regional Director of R & D for the North Thames Region from 1996. Sally has been actively involved in NHS R&D from its establishment, previously chairing the Regional Responsive Funding Group.

Her own research interests focus on the haemoglobinopathies, in particular Sickle Cell disease, leading studies ranging from the molecular level to surveying the community response to screening programmes. She continues to lead this programme actively, with collaborations across many professions, both inside and outside Britain. Sally is editor for the Haemoglobinopathy section of the International Cochrane Collaboration. She also continues weekly paediatric and adult haemoglobinopathy clinics at Central Middlesex Hospital Trust in Brent.

Clinical research is in a time of change. People involved in clinical research will be aware of a lot of barriers to research, including increased regulations and its consequent bureaucracy as well as service pressures.

Targets have taken people's efforts and perspective away from clinical research. We've had decades of underfunding, which has eaten away at the infrastructure of clinical research. We have the introduction of new contracts for consultants, GPs and primary care. One of the biggest barriers is the levers and incentive system in the NHS: the incentive system is about leadership of research, and a lot of people want to do small trials that aren't always methodologically sound and often won't answer the question. So it's important that we encourage collaboration and have just a few leaders who work out the research protocol, then lead the research and analyse the results, with the majority of people working on the collaboration side. So capacity is in short supply and there are a number of other changes that are happening now, such as the introduction of Foundation Trusts and from April 2005, 'payment by results'.

Reports show the way forward

There have been two very important reports on the subject of clinical research which have set the agenda for the way forward.

First, 'Strengthening Clinical Research', published in October 2003, is from the Academy of Medical Sciences, containing four key recommendations:

- Setting up a national clinical research network
- Improving clinical career structures and incentives
- Improving the regulatory environment
- Increasing NHS R&D funding (aiming at 1.5 per cent).

Second, 'Improving National Health, Improving National Wealth', published at the same time, is from the Bioscience Innovation and Growth Team. It argues for:

- A National Clinical Trials Agency
- An environment supportive of innovation
- Investment in public R&D infrastructure
- Building a bioprocessing subsector
- The development and training of talent.

Working together

There are other drivers for change. There is the industry lobby, first represented by the Pharmaceutical Industry Competitiveness Task Force and now the present Healthcare Industry Task Force. We have a big agenda in common between industry and clinical research, and if we don't work together, and the if NHS doesn't deliver, we will lose an important source of income and of academic understanding, and we will be poorer in the NHS, in our

universities, and as a society. It's important to get the right networks going and do the job properly. In this area of clinical practice, we are shoulder to shoulder with industry.

The Government wanted to respond and asked Sir John Pattison to set up a group called the Research for Patient Benefit Working Party. Many people worked on this and the result was to recommend the creation of a UK Clinical Research Collaboration (UKCRC) to oversee the effective and efficient translation of scientific advances into patient care, resulting from expanding and developing the clinical infrastructure embedded in the NHS.

A model partnership

The model for this was the National Cancer Research Institute (NCRI), a partnership between all major cancer research funders (government, NGOs and industry) to take a strategic oversight of cancer research in the UK. It is a 'virtual' organisation, involving a range of stakeholders. The National Cancer Research Network (NCRN) is a 'managed research network' that maps onto all 34 cancer services networks across the country and provides the NHS infrastructure for randomised controlled trials and other well-designed studies. An experimental translational research network, the National Translational Network for Cancer (NTRAC), has also been set up, which the NCRI is currently reviewing.

More investment

The Secretary of State for Health, Dr John Reid, has confirmed that for the Government, "science and research constitute a frontline service, as they, too, reduce distress and pain and save lives". As a consequence, there has been the largest-ever sustained increase in Government funding for health R&D.

We all know the advantages of clinical research, but we are going to have to state them and restate them with clinicians so that they join in. The broader task is to change the face of research in the NHS. The argument for investment came through the Spending Review and in July 2004, the Treasury and DTI published the Science and Innovation Investment Framework for 2004-2014. In it, the Government states that its ambition is "for the UK to be a key knowledge hub in the global economy… and at the core is R&D capacity… which enables it to create, absorb and deploy new ideas rapidly".

Introducing the UKCRC

Within this framework comes the UK Clinical Research Collaboration. It brings together a range of members – the Department of Health, the NHS, the Medical Research Council, the Wellcome Trust, academic institutions, the pharmaceutical industry, the Association of Medical Research Charities, patients and others. Its role is to:

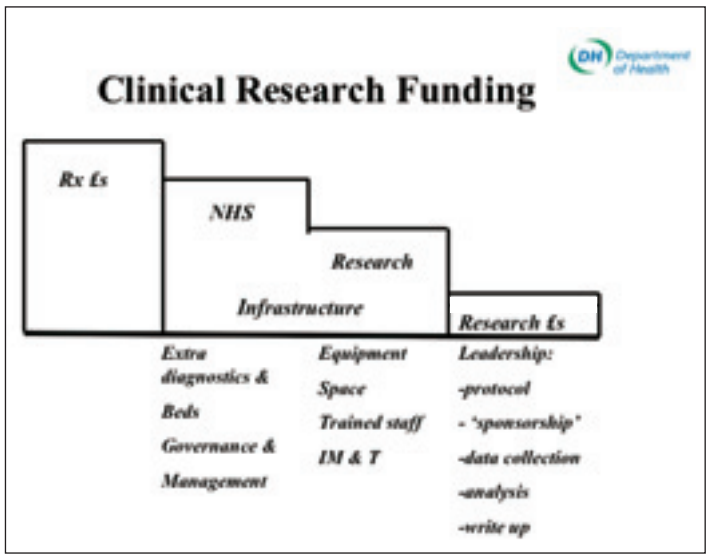
- Take a strategic oversight of clinical research
- Identify gaps in infrastructure and programmes
- Identify opportunities for action
- Work to negotiate solutions
- Plan and co-ordinate.

The UKCRC has a number of workstreams:

- To develop NHS-based clinical research
- To increase UK clinical research activity
- To improve incentives and remove barriers within the NHS
- To sort out academic careers and training
- To work for 'Better Regulation'.

The UKCRC has an agreed style:

- Add value
- Balance communication with momentum
- Build on what is working well
- Engage stakeholders through consultation and negotiation, not representation
- Provide a solutions-based approach, not just recommendations
- A core team, drawing on expertise and leadership of partnership organisations
- Intend to evaluate the impact of the organisation.



It is important to be clear about the different bits of funding that go into clinical research. If it's a study being funded by industry, the same elements are there (box above), but will work out slightly differently. First, there is money for treatment, which in public sector research is in the NHS and paid for as part of the service. Then there are two types of infrastructure – NHS infrastructure and research infrastructure, for which the NHS rightly pays a proportion. Research grants will continue to pay for the leadership aspects. This won't make the studies cheaper, but it will make them faster and more effective, help them to be carried out to better standards.

The UKCRC now intends to expand its clinical networks from cancer to set up new networks for diabetes, children, stroke and Alzheimer's and to expand the existing mental health network, with more to follow.

This becomes a very complex mixture. Using the cancer research networks as a model, we've asked the question: who gives the direction? Strategic direction comes from the UKCRC for all these networks in general, delegated down to the 'Funders' Fora', which will report into the UKCRC. There will be a national co-ordinating centre for the Clinical Research Networks. Processes for setting these up are taking place now.

Clinical Research Networks

The disease specific networks, probably of about eight centres in each research area, are managed networks rather than academic networks. By competition, the Department will agree a lead, who will be a national subject specialist and who will recruit further enthusiasts. We shall be looking at whether the national co-ordinating centre will be able to commission a national data capture system, and setting up a network of regulatory expertise and advice, as well as supplying training support on a national level.

The key aims of the Medicines for Children Research Network are:

- To establish a UK presence in advance of EU regulation
- To facilitate randomised clinical trials and other well-designed studies of medicines for children, including those for prevention, diagnosis and treatment
- To remove the NHS barriers to each resource
- To involve primary care.

This is different from earlier networks, and the model will be different for each area. The Children's Network Co-ordinating Centre will be expected to:

- Establish and lead the network
- Manage the network to maximise its impact
- Promote the active involvement of its partners
- Contribute to the wider aims of the UKCRC.

A future need will be to measure our success, because if we can't prove to the Government what we have achieved we may end up not getting any more money in the future. Aspects of this involve clinical trials and the number of patients entered, publications and patents. The Government will be reviewing the activities of the UKCRC.

Public health, parent's reality

Kedge Martin, Chief Executive, Wellchild

Kedge Martin started her career in political lobbying and as a part-time research assistant to an MEP before moving into the travel industry. In 1991, she relocated to newly liberated Poland where she set up and ran a chain of launderettes and dry cleaners. On her return to England, Kedge worked as Campaign Manager for the NSPCC London Full Stop Appeal before joining WellChild as Chief Executive. Based in Worcestershire, she is mother of two children, and is fervently committed to all issues affecting child welfare – both social and health. She is trustee of the Association of Medical Research Charities (AMRC) and a governor at her local school.

Wellchild was established in1977 and since then has invested more than £30 million into medical research projects throughout the UK. Our research objectives are to support young researchers with innovative ideas who can then progress to long-term funding from larger funders. Wellchild also provides support and information for parents and children through a website **www.childrenfirst.co.uk** developed in collaboration with Great Ormond Street Hospital and a helpline for families, children and carers – 0845 122 8636.

Children's health needs more research

There are 15 million children in the UK. One in five has a long-standing illness or disability. Many of them may be on some form of medication that may yet be unlicensed, and of which the long-term benefits or side-effects are not yet scientifically established. That's playing roulette with the health of children. So the forthcoming legislation to encourage well-managed, well-regulated and ethically responsible clinical trials to develop medicines specifically for children is a welcome step.

Parents are generally positive about being involved in clinical trials for their children. They weigh up the risk/benefit and they are more willing to be involved if their child is acutely sick. They also believe that they get access to better healthcare, including more time with healthcare professionals. A further aspect is that they feel they are taking control over their child's illness by positively being involved. They feel that they are helping other children in the future, and there is a great deal of comfort gained from meeting families in similar situations.

In 70 per cent of cases, it was the mother who made the decision to enter her child in a clinical trial, rather than the father or both parents.

Generally, feedback from the children has been positive, and every child we've spoken to has had a feeling of altruism about their involvement. They feel more empowered about their treatment and meeting and talking to other children in similar circumstances is also very important to them.

Problems

Of course, there are some concerns and criticisms relating to the trials. These include:

- Discomfort to the child, especially in invasive treatment
- Inconvenience in terms of time and interruption to normal routines
- Financial impact
- Known and unknown risks
- Why mess with success if the current treatment is going well?
- Lack of on-going information
- Lack of feedback on trial results
- Doctors are more focused on the research, rather than on the care of the child.

Some of these were serious reservations – for example, half the parents asked would not want to take part in further trials because they felt that once engaged in the trial they had not received adequate information during the trial and little or no feedback on outcomes.

Getting people involved

There are ways to encourage more participation in trials. We need to provide access and information on existing and forthcoming clinical trials. We need clear guidelines for compensation for the time and costs involved. Parents' expectations need to be managed, and it should be explained that trials are not a cureall. Information and feedback about the trials while they are still running and at their conclusion is also crucial. We need to encourage doctors who are not part of the trials to encourage participation. More importantly, the general public should be educated about the rationale and benefits of participation in clinical trials.

In conclusion, families and children are supportive of research. We need to be aware of the various cultural issues involved. Trials need to be developed in partnership with the families. Clear information at the outset is very important, as is information during the trials and at their end. We need clinical trials of routine clinical care now as well as trials for new treatments. Every child deserves the best possible treatment and care and it is all of our responsibility to provide it.

Why the issue of medicines for children has come up the agenda

Dr Julia Dunne, Post-Licensing Division, Medicines and Healthcare products Regulation Agency

Dr Dunne is qualified in medicine and worked in the NHS before joining the Medicines Control Agency (now the Medicines and Healthcare products Regulatory Agency) in 1990. Dr Dunne held posts as a medical assessor (new chemical entities), unit manager (new chemical entities) and acting group manager (Licensing Division).

Julia was seconded twice to the European Commission (Pharmaceuticals Unit, DG Enterprise), first in the early 1990s and most recently from 2001-2003, when she worked on the Commission proposal for a Regulation on paediatric medicines. Back at the MHRA since September 2003 and now in the Post-Licensing Division, Dr Dunne continues to work on paediatric issues, including the UK strategy on medicines for children and the Commission proposal, as well as having certain pharmacovigilance responsibilities. Dr Dunne is also the UK alternate delegate to the EU's Committee for Medicinal Products for Human Use (CHMP).

In October 2004 the European Commission adopted a proposal for a Regulation on medicines for paediatric use. A simplified version of the European legislation process is as follows: the European Commission makes a proposal which is then considered separately by the European Council (the Member States) and the European Parliament who each may propose amendments before final agreement. The elements currently set out in this proposal, therefore, may change before the Regulation is finally adopted. Although the Commission proposal was adopted at the end of September 2004, the need for European legislation in this area has been under discussion for about seven years.

The objectives of the proposal are to:

- Increase the development of medicines for children. (For the purposes of the discussion, the term 'children' covers the ages from 0 to 18. There are, however, subgroups within the age range as defined by ICH guidance.)
- Ensure high quality research into medicines for children
- Ensure appropriately authorised and formulated medicinal products for use in children
- Improve the information available to patients, carers and prescriber. (including information on why the use of the medicine is not recommended) at the same time as avoiding subjecting children to unnecessary clinical trials.

Paediatric Committee

The proposal establishes a new European Paediatric Committee within the European Medicines Evaluation Agency. The Committee would comprise members with expertise in areas relevant to paediatric medicine and would be made up of a number of members from the CHMP, representatives from the Member States and stakeholders nominated by the Commission (paediatricians from European Paediatric Associations and representatives from patient organisations). The Committee's tasks relate to the objectives of the proposal, but the most important one would be to examine and agree the Paediatric Investigation Plan (PIP), which would be a requirement for new products.

Paediatric Investigation Plan (PIP)

The proposal establishes a requirement for applications for marketing authorisation for new medicines to include the results of an agreed paediatric investigation plan. The plan would relate to all appropriate age groups for the product. The requirement does not apply to generics, herbal or homeopathic products or products claiming 'established use'. But it does include applications for existing products still covered by a patent, where these are for new indications, new pharmaceutical forms or new routes of administration. There would be a possibility of a deferral from the requirement to include the results of the plan at the time of the marketing authorisation application, but the application would have to contain the agreed plan with a timetable for completion of the studies. A waiver could be granted if it were considered that the product would not be appropriate for use in children, would be unsafe or ineffective, or that paediatric use is sufficiently covered by existing licensed products in the particular therapeutic area.

The plan would ensure the availability of data on the use of the product in the relevant groups of the population and on appropriate paediatric formulations. It would be submitted to the Paediatric Committee prior to the submission of the marketing authorisation application. The Paediatric Committee would consider all aspects of the plan and the expected therapeutic benefit. It may request modifications of the plan, may grant a waiver or a deferral and would give a positive or negative opinion. The marketing authorisation holder may appeal against the decision. The agreed plan would then serve as a basis for evaluation of that aspect of the marketing authorisation application.

The proposal does not give much detail about the content of the PIP, this will be left to implementing guidance. However, it is likely that the PIP will be a detailed document.

Benefits for companies

There will be access to the centralised procedure for medicinal products for any application which presents the results of a PIP, and this will apply to new products and to Paediatric Use Marketing Authorisations (PUMAs – see below). This would help companies, especially smaller ones, to obtain an authorisation in all EU markets.

There is an incentive for new products – a six-month extension of the duration of the period in the Supplementary Protection Certificate if a certain number of criteria are fulfilled. The marketing authorisation application must include the results of all the measures in the agreed PIP, or they must have been submitted following first authorisation in the case of a deferral. The relevant information from these studies must have been incorporated into the Summary of Product Characteristics (SmPC) and there must be a marketing authorisation in all Member States. The MAH is entitled to the six-month extension whether or not a paediatric indication has been granted, provided that the criteria are fulfilled, including the inclusion of the relevant paediatric information in the SmPC.

A similar situation would apply for orphan products. If the above criteria have been fulfilled, the incentive would be an extra two years' market exclusivity, from 10 to 12 years.

Paediatric Use Marketing Authorisation

For existing products which are off patent, the proposal establishes a new type of Marketing Authorisation, called a Paediatric Use Marketing Authorisation (PUMA). This would apply to off-patent products for which a paediatric indication had been developed according to an agreed PIP. An application for a PUMA would be eligible for the centralised procedure. There would be 8 years' data protection and 10 years' market protection covering the paediatric studies and any paediatric formulation specific data. This is similar to the current situation for new products. Member States may consider creating national incentives to encourage the development and use of PUMAs.

Safety and information aspects

Other elements of the proposal include post-marketing requirements, especially for the long-term safety of products, and effective paediatric pharmacovigilance. The Paediatric Committee would draw up an inventory of therapeutic needs to help prioritise work and to aid decision-making. The proposal establishes a paediatric clinical trials network at a European level, separate from national networks and co-ordinated by the EMEA, and a European paediatric clinical trials database. In earlier drafts of the proposal, relevant parts of the database would be publicly accessible – but this has been dropped from the adopted proposal. Given the current interest in increased transparency, it is possible that Member States or the European Parliament would try to restore the partial public accessibility of the database. The Paediatric Committee would give free scientific advice on paediatric product development. Paediatric clinical trials completed before the Regulation entered into force would be submitted to the authorities in the EU for assessment.

The Paediatric Study Program, which featured in earlier drafts of the proposal, was dropped from the final proposal because of legal and other difficulties. The Program will be developed separately, either through another piece of legislation or by some other means.

Next steps

Following adoption of the proposal, the Member States will begin formal consideration of the text, as will the European Parliament. Only then will it be possible to see how quickly the proposal might progress. The UK hopes to make significant progress during its Presidency in the second half of 2005. However, it is unlikely that the Regulation will be finalised before the end of 2006.

The ethics of doing paediatric clinical trials

Dr Hugh Davies, Training and Ethics Advisor, Central Office for Research Ethics Committees (COREC)

Hugh Davies is a consultant paediatrician working in a district general hospital in Northwest London. From 1989 to 1993 Dr Davies was a member of the St Mary's Hospital Paddington Research Ethics Committee and from 1994 to 1997 chair of the Brent Research Ethics Committee. From 1997 to 2002 he was chair of the North Thames and then London Multi-centre Research Ethics Committee.

Since then, Dr Davies has been training and ethics advisor to the Central Office for Research Ethics Committees (COREC), the body charged with supervision of Research Ethics Committees (RECs) in the United Kingdom. In this capacity he has undertaken the establishment of a national training programme for members of these committees and has also worked with the ABPI to provide insight into RECs and their work, particularly for industry researchers.

There are as many guidelines and recipes in issues involving research ethics as there are cookbooks – a wide range of relevant material is available from the World Health Organisation, the Royal College of Paediatrics and Child Health (RCCPH) and on databases such as **www.eric-on-line.co.uk**.

While the primary purpose of ethics committees is to protect the rights, safety, dignity and wellbeing of research participants, it seems to me they have a broader role in joining the debate on how ethical research involving children can be facilitated. To this end, I have worked to bring together researchers and reviewers so they may identify barriers to such research and potential solutions.

It's very difficult to provide broad guidance for any group of researchers, particularly in research involving children. If there is a single message from the "REC community" to researchers, it is that we look for "the reasoning researcher" who will look at the study from the children's and parents' point of view – one who addresses the ethical issues from the very beginning and goes beyond "cutting and pasting" guidelines.

As ethical issues have no straight forward solutions, I see guidance in the form of *"Issues and Arguments"* that avoid proscriptive solutions but provide broad boundaries agreed through consensus.

There are some key areas at the centre of research involving children.

The need for research involving children

This need is well established, but ethics committees look at the likely benefits and depending on the perceived benefit, evaluate the impositions of a study before them. A researcher should thus be well versed in why he or she wishes to undertake the study.

Risk

Participation and the protection of children in research brings up the matter of risk. The Federal Drug Administration in the USA identifies four categories of risk, ranging from minimal risk to more invasive research, and provides guidance on how each should be reviewed. In the UK, the RCCPH uses simpler definitions of minimal risk, low risk and high risk. Where children are exposed to more than minimal risk, the college argues that such research deserves serious ethical consideration, but goes no further.

Consent

Researchers need to ensure that they have the personnel in place who can assess competence and are trained in such

issues as competence and consent. Where children have sufficient understanding and intelligence to understand what is proposed, it is they and not their parents whose consent is required. If there is a conflict between the opinions of the child and the parents, and this is rare, the child would not normally be recruited.

There is no particular agreement about the area of children and non-therapeutic research. Perhaps it is only allowable when the risk is less than minimal, but trials of new oncology treatments raise difficulties that probably need to be considered case by case. The use of a placebo is not ruled out, but will need to be agreed before the research is carried out.

Rights and duties

There is an opinion abroad that children and their parents have the right to properly researched medicines. Consequently, there are now pressures on researchers to undertake research involving children; the USA and soon the EU will put financial incentives in place. My view is that researchers will be vulnerable to the rather protective and rights-based attitudes in society.

But any right has a corresponding duty – one cannot exist without the other. In the current climate, we emphasise the rights of children and parents. If they have the right to appropriately trialled medicines, is there an associated duty to be involved in trials, and how should families discharge this duty? I have no answer, but feel it needs a broader audience. Such discussion will give researchers who wish to undertake research involving children help and guidance.

In conclusion, there is useful guidance available but ethics committees are not looking for someone who slavishly follows a recipe. We look towards the reasoning researcher – someone who, when designing a project, looks at how it appears from the point of view of a parent or a child, how their needs are accommodated, how the child will be protected and how the parent will be provided for.

Paediatric clinical trials from an industry viewpoint

Dr Richard Tiner, Director of Medicine, Association of the British Pharmaceutical Industry

Dr Richard Tiner is the Director of Medicine at the Association of the British Pharmaceutical Industry (ABPI). He qualified in medicine in 1974 and following junior doctor posts in Kettering and Taunton, he worked as a Principal in General Practice in Somerset for 17 years.

In 1996 he joined the ABPI as Medical Director and his current responsibilities include NICE Clinical Guidelines, regulation of clinical trials, development of paediatric medicines, liaison with medical organisations, antibiotic resistance and cancer. He is also a non-executive director of MLI Ltd, a not-for-profit company that investigates research misconduct.

Paediatric research is not a new issue. In 1996, the ABPI and the British Paediatric Association published a joint report called *Licensing Medicines for Children*. It called for medicines to be licensed for specific age ranges, the development of clinical research guidelines, and for the Committee on Proprietary Medicinal Products (CPMP) to produce guidelines for paediatric clinical research.

The CPMP published voluntary guidelines in September 1997, but they have not led to much increase in paediatric research. One other major event was the publication of guidelines on sponsored research in children by the International Conference on Harmonisation in 2001 (ICH E11). Its focus on pharmacokinetics is likely to be an important feature of children's studies in the future, along with its definition of children's age groups from neonates to adolescents.

The need for paediatric research

Why are paediatric studies needed? More than 90 per cent of medicines used in neonatal care, 45 per cent of medicines used in general paediatric care, and between 10 and 20 per cent of medicines used in children in general practice are actually used off-label or are unlicensed. So it's a very common practice that many medicines are used that have no indication for use in children.

But there are issues for the industry in this area. There are many millions of children in Europe, but the overall paediatric market is small. One ABPI member has estimated that to fully develop a Paediatric Investigation Plan would cost approximately €20million. For an existing product, that could turn out to be a poor to moderate, or even negative, return on their investment.

More medicines for children

The objective of the proposed Regulation is to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children. It has requirements for industry and also introduces incentives, as we have already heard.

Children will undoubtedly have access to more licensed medicines through the implementation of the proposed Regulation. However, it is not sure that the incentives will lead to more paediatric research in Europe, since the extension period is no advance on the current American position. It is also unlikely that older products will undergo more research, which is unfortunate, as many paediatricians would like to see more research into existing products. The opportunity for setting up a central fund has been shirked by the Commission. The industry is unlikely to carry out research in these older products, especially as the originators do not own those products any longer and

generic producers have no tradition of research. This will become a real issue in future.

If more research in Europe takes place, it will probably not happen until the Regulation passes into law. Incentives are important, but should be longer than six months' patent extension, and transitional incentives with a meaningful effect should be introduced as soon as possible. There are precedents for this, and the Commission could have introduced recommendations from the day the proposal was published for new research in medicines for children. Incentives to achieve this should also be competitive with the US (i.e longer).

Support for clinical trials

Progress in supporting paediatric trials is being made. The ABPI helped to fund one of the reviews of paediatric clinical pharmacology (the 'Lilleyman Report'), published in the summer of 2004, which recommended setting up a UK paediatric clinical pharmacology network. The ABPI is a member of the UK Clinical Research Collaboration Board, which should help to encourage the growth of the paediatric research network once the co-ordinating centre has been appointed. For many years, the ABPI has been supporting clinical pharmacology in the UK and has supported 22 training posts, two of which are in paediatric clinical pharmacology. One further area which the industry is supporting is the School of Pharmacy Pharmacoepidemiology Database, launched a year ago.

The ABPI is a member of the Priority Action Team of the European Federation of Pharmaceutical Industry Associations (EFPIA), which brings the whole of the European industry together. The law will apply right across Europe, so a combined European industry response will be necessary. Similarly, the ABPI has set up its own UK Working Group which will shadow the EFPIA efforts, and to look at issues of paediatric medicines which are relevant in the UK.

There will be more licensed medicines for children as a result of these activities. We hope that the UK will attract more paediatric clinical trials, but we cannot be certain that it will. Most importantly, we hope that the remaining legislative process will be completed as quickly as possible. The original proposal was made in December 2000, and now it needs to be brought into law.

Discussion sessions

During the discussions which followed the presentations, a number of points were raised and debated. What follows is a summary only and the ideas below came as much from the floor of the conference as from members of the panel.

Are we putting too much emphasis on the pharmaceutical aspects of paediatric research?

Medicines are a good starting point for attention. The Government has to decide the priorities and financial resources are limited. Paediatric research networks are a good basis and it is to be hoped that growth in this area will attract other research as well.

For 75 million children in Europe, there are just 45 clinical pharmacologists with an interest in paediatrics. How can we expect to get things done?

Most clinical trials take place without a clinical pharmacologist. We can still cope with the present capacity as we build up the infrastructure, but of course, there is a need for more specialists in this area.

Can extra information about paediatric studies be included for older products?

Companies already scan the literature for information about their products and the MHRA is very sympathetic to receiving such information, and has licensed products based on published information and data on file. Companies might then be able to make available why a product is or is not suitable for children. Admittedly, this does not appear to have been tested yet. The clear aim is to protect patients.

Will the findings of the European Paediatric Committee be published?

Currently, the meetings are closed, for commercial and confidentiality reasons. The EMEA publishes a report after CHMP decisions, so it might do the same for the EPC. The proposal is not clear about this aspect, but it is unlikely that reports will be published.

What discussions have taken place regarding the setting up of a dedicated paediatric register of clinical trial?

The World Health Organisation is expected to make a statement about the registration of clinical trials, although it will not be restricted to paediatric trials.

Governments will be expected to sign up to a more open availability and registration environment. A condition of funding may be the registration of a clinical trial. The ABPI has a retrospective and voluntary database of clinical trials, which it will be reviewing on a regular basis.

How can we deal with such a wide range of conditions and assess them properly?

In the European Paediatric Committee, members can call in the experts in the field, specialists from the CHMP, patient representatives and paediatricians who can be invited to discuss the particular issue. In Britain, the forthcoming publication of the Children's British National Formulary will also be a help. It will list unlicensed uses for authorised medicines. The ABPI supports this idea in principle, although it creates problem for its member companies, who are not allowed to promote their use in unauthorised indications.

What are the ethics of putting children with life-threatening conditions into high-risk clinical trials?

The Child Cancer Study Group, for example, has found it useful to work with a single ethics committee, which helps to build up experience of the issues involved. Guidance suggests that paediatric experience is required if paediatric issues are involved, but too many 'specialist' committees may lead to a proliferation of this type and a reduction in the number of more generalist committees. Lord Warner has announced a review of ethics committees, to be published by April 2005, so there is an opportunity to submit some thoughts now.

How can it be ethical that children in the UK are in approved clinical trials involving orphan drugs and yet they can't subsequently get funding for their treatment from their local PCT?

There are two questions here. One is about licensing and the other is about cost-effectiveness. If a product has not been licensed, how do we go about funding it? We need to get money to evaluate the product, and this comes in the research process. Then NICE needs to be convinced that it is cost-effective. There is no doubt that postcode prescribing is still an issue, but there are no easy answers to this question, especially as orphan drug treatments are often very expensive.

How can we square that with parents with children in clinical trials?

Parents need information. If the medicine is never going to used after its clinical trial, then researchers must make that clear. If the research has at least been done, we will be in a better position to evaluate the medicine and submit it to NICE. If the clinical trial has been done and the medicine has not yet been licensed, it will probably be available until the authorisation date. But after authorisation, it becomes the Department's responsibility to decide on reimbursement issues. Expensive orphan drugs can cause a problem. In Scotland, they are likely to be made available under a central fund so that costs do not impose strains on local budgets, and perhaps this is a way forward elsewhere.

Insurance problems

Insurers are reluctant to provide cover for universities carrying out clinical trials for children and pregnant women. This seems to apply across the UK. Pharmaceutical companies have also experienced problems in these areas. This will be an issue for the Paediatrics Network of the UKCRC.

Clinical Trials – developing new medicines

In the search to understand, prevent and treat disease, clinical trials involving healthy volunteers and patients play an essential role. Their aim is to evaluate new medicines or a combination of medicines, as well as other types of therapies, to determine their potential benefits and safety.

- **Nearly a quarter of the world's top 100 medicines were developed in the UK.**
- **Attracting clinical trials to the UK is important for patients, for the NHS, for academia and for the nation's economy.**
- **Studies have demonstrated that patients taking part in clinical trials have better health outcomes than those not involved in a trial.**
- **Clinical trials mean that NHS patients have potential early access to the newest forms of treatment together with the highest standards of medical care.**
- **Clinical trial participants must have given their informed consent and confirmed they have received and understood full information before they can take part in a trial.**
- **A company must provide all results from the trials when applying for a licence for a new medicine.**

The prime sponsor of medicines research in the UK is the pharmaceutical industry, but research charities, Research Councils and the NHS also undertake medicines research.

A new medicine has to demonstrate its safety, quality and efficacy through a series of rigorous clinical trials in order to obtain a licence (called a marketing authorisation) and be available to the general public.

Clinical trials consist of four phases – the first three occur before a licence is granted and the last is conducted as a post-licensing phase. Each phase varies in size, character and focus:

- **Phase 1** primarily determines how a medicine works in humans and helps to predict the dosage range for the medicine,and involves healthy volunteers.
- **Phase 2** tests efficacy as well as safety among a small group of patients (100-300) with the condition for which the medicine has been developed.
- **Phase 3** involves a much larger group (1000-5000) of these patients which will help determine if the medicine can be considered both safe and effective.

THE BENEFITS OF CLINICAL RESEARCH IN THE UK

Nearly a quarter of the world's top 100 medicines were developed in the UK, which is a leading centre for clinical trials. However, trials are increasingly conducted around the world, in order that greater numbers of patients and different ethnic groups can be included in a study.

Attracting clinical trials to the UK is important for patients, for the NHS, for academia and for the nation's economy. Their presence means that NHS patients have potential early access to the newest forms of treatment, together with the highest standards of medical care. But these studies are also important because they bring investment into academic research centres in the UK. Researchers are provided with the opportunity to be at the centre of the development of the latest medicines, benefiting the quality and depth of science research in this country.

The cost of developing a new medicine is about £500 million – 60 per cent of which is spent in clinical trials – and the full development process takes 10-12 years.

New medicines are selected from a range of many thousands of substances with the potential to treat the targeted condition. Fewer than one or two compounds in 10,000 tested actually make it through the process and are eventually authorised for use in patients – a potential new medicine may be rejected at various stages in the development process on safety, efficacy or quality grounds.

A new medicine arises from a series of pre-clinical tests – using techniques which identify potentially beneficial new compounds, like computer modelling, high-speed computer technology and tissue culture studies. It is then tested in a series of scientific studies using animals before any trials involving humans.

DEVELOPING A PROTOCOL

Having decided clinical development is justified, clinical researchers will need to develop protocols for the necessary trials. A protocol is a study plan which is not only designed to answer specific research questions but also has the safety of participants in mind. Used as the

basis for all clinical trials, protocols determine:

- Who can participate.
- The schedule for tests, dosages and other details of the study.
- The trial duration.

FINDING AN INVESTIGATOR

Once the protocol has been established, a trial then needs investigators (clinical researchers) to carry out the study. Investigators are doctors who work with a team to monitor and care for the patients involved in the studies.

They usually come from universities or from within the NHS – including GPs – and become involved because they have specific expertise in the clinical area under investigation; they are directly approached by a sponsor or have expressed an interest in being involved.

Any NHS clinical researcher who acts as an investigator for a pharmaceutical company-sponsored clinical trial will receive payment from the company, via their NHS trust, for the work they have done – much as with government-sponsored Medical Research Council trials, where a research grant will cover the cost of paying for staff and for the researcher.

In the UK, under the Research Governance Framework, all receipts go through an NHS or primary care trust and any benefits of more than £25 must be declared.

TRIAL APPROVAL

With doctors appointed, clinical trial sponsors must meet strict regulatory requirements. This means they need to demonstrate to the regulatory authority – the UK Medicines and Healthcare products Regulatory Agency (MHRA) – that they have a reasonable hypothesis upon which to base the study and that pre-clinical results warrant further research.

Details of all trials conducted within the UK must also be approved by independent research ethics committees before work starts. Additionally, sponsors must receive approval from the NHS trust in which the trial is being conducted.

Ethics committees review and advise on whether proposals for research studies meet required ethical and scientific standards. These reviews are designed to protect people participating in studies.

Ethics committees are completely independent of industry and are at liberty to reject a clinical trial. They are established and funded by the NHS, while remaining health authority based. Typically consisting of between 12 and 18 members, they include lay people, medical professionals, and scientists. Once approved, the process of selecting participants for the study begins.

SELECTING VOLUNTEERS

The first stage in which humans are used in the study of a new medicine is Phase 1. Participants in these trials are usually healthy volunteers under 45 years.

Participants in Phases 2 and 3 are patients with the medical condition for which the new medicine is being tested. However, like Phase 1 participants, they can only take part in a clinical trial on a voluntary basis.

Additionally, these volunteers – whether they are healthy participants or patients – can only participate in clinical trials if they have given their informed consent and have confirmed they have received and fully understood information about the trial. They are also free to withdraw from a trial at any time without prejudice to their continuing care.

A number of studies have demonstrated that patients taking part in clinical trials have better outcomes than equivalent patients not involved in a trial. This is because the trial patients are receiving close and ongoing medical care.

Guidelines have been set on the processes involved in clinical trials on medicines by the International Committee on Harmonisation (ICH) – a series of joint agreements between the regulatory authorities and the representative pharmaceutical industry groups in Japan, Europe and the US. The principles of these guidelines, known as Good Clinical Practice (GCP), will be enshrined in UK law for implementation from May 2004.

Patients taking part in Phases 2 and 3 are invited to participate in three main ways:

1. Advertising is mostly placed at a local level – using both newspapers and radio stations or through hospital and GP surgery notice boards.

2. Patient groups may also be a means through which patients learn about clinical trials. These groups are often well informed about research being conducted in their area of interest.

3. An invitation is the most common method of recruitment – usually through doctors who are involved in, or aware of, a trial that would be of relevance to, and in the interest of, a patient.

Before a participant enters a trial, a trial team will check and record his/her health. Each participant will then be closely monitored throughout the study and will continue to have some contact from the research team after the trial is finished.

A potential treatment will be constantly monitored in an

attempt to optimise its effectiveness and reduce any side-effects.

Throughout the process, data is collected and recorded for analysis to evaluate the patient's response. However, only the investigator and his team will know the identity of the patient; the sponsoring company will have only a patient code number to bring all the individual patient data together.

CONTROL GROUPS

Most trials will involve some sort of comparison for the medicine being tested. This means that in many clinical trials, while one group of patients will be given an experimental medicine or treatment, a control group is given either an existing standard treatment (comparator) for the illness or a placebo – a dose that looks like the medicine being tested but, in fact, contains no medical ingredients.

Regulatory authorities have complete power to require a comparison to be carried out and suggest either a placebo or specific comparator product.

It is more common for such a control group to use a standard existing treatment for the studied condition as its comparator substance. However, as many trials are multinational, it may be that the comparator is not always the most commonly used treatment in all of the countries involved in the trial. The choice of which medicine to use as a comparator can be influenced by many factors, including the comparative sizes of the different countries' trials groups, the location of the medicine's pre-clinical development or the intended location for a licensing application.

Placebo trials tend to be most common in the US, which uses them more than the UK. The Food and Drug Administration (FDA), the US regulatory authority, prefers the use of placebos to comparator substances because it is often a more rigorous way of determining the difference between results. In Europe, however, most ethics committees favour the use of comparators, which they see as more ethical.

REGULATION AND MONITORING

All trials must be performed in line with ICH GCP principles or they will be rejected by the regulators. Clinical trials in the UK are also conducted according to a series of guidelines and regulations laid down by government authorities, including the NHS Research Governance Framework and the guidance provided by ethics committees – all of which are underpinned by the Declaration of Helsinki.

If a patient has concerns about any aspect of a trial, they have numerous avenues through which they can lodge a complaint. These include ethics committees; the research centre's administration; their GP; patient groups; the research sponsor; and the ABPI.

TRIALS AFTER A LICENCE

Phase 4 trials are conducted after a medicine has been granted a licence. In these studies a medicine is prescribed in an everyday healthcare environment which allows results to be developed using a much larger group of participants. Phase 4 trials are performed to:

- Develop new treatment uses for the medicine.
- Compare with other treatments for the condition.
- Determine the clinical effectiveness of the medicine in a much wider variety of patient types in conditions of "real life".

Safety is a major part of Phase 4 trials, which often involve several thousand patients so that that more rare side effects, if any, may be detected.

In addition, because larger numbers of patients can be studied, doctors are able to monitor quality of life issues, and other benefits of the medicine may become evident.

As with all phases of UK clinical trials, there are strict rules regarding the way in which Phase 4 studies are conducted. In particular, this means they cannot be used for anything other than a scientific purpose – for example, as a promotional tool for the product.

PUBLISHING TRIAL RESULTS

After a trial is complete, doctors will seek to publish the information in a medical journal. This is primarily so that other doctors and scientists can benefit from the research findings and be aware of potential new treatments.

When a trial fails to show positive results, it normally does not make interesting news and medical journals often do not publish them. The industry believes that these 'negative' data should be made available and so the majority of the trials not accepted in peer reviewed medical journals are published in other ways through supplements to journals, clinical reports, conference posters, abstracts and on the internet.

When a licence application is submitted, a company must provide all results – both positive and negative – from the trials. A summary of this information is available to the public through European Public Assessment Reports (EPARs), produced by the European Medicines Evaluation Agency (EMEA) on the granting of a licence.

In line with this, the ABPI has established a special website for companies to publish information about clinical trials conducted for licensed medicines. The website provides a readily accessible list and information about which trials have been carried out and in which therapeutic areas. The site is not only intended for healthcare professionals, but will also be of use to patient organisations and the public.

Details are supplied on a voluntary basis by companies and can be found at https://www.cmrinteract.com/clintrial/

CONCLUSION

The UK has traditionally been a leading nation in medicines development and clinical research, largely by providing the highest standards of scientific research and medical care. The treatments discovered and developed are vital because they have helped save lives, reduced suffering and improved the quality of life for millions of people all over the world.

This section is published separately as an ABPI Briefing Paper

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.

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

The 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.

This section is published separately as an ABPI Briefing Paper

Useful information

www.abpi.org.uk	ABPI's main website, links to other related sites
www.dh.org.uk	Department of Health's main website
www.mhra.gov.uk	Medicines and Healthcare Products Regulation Agency
www.corec.org.uk	Central Office for Research Ethics Committees
www.eric-on-line.co.uk	Articles on medical research
www.wellchild.org.uk	Charity for children's health and wellbeing
https://www.cmrinteract.com/clintrial	Lists details of current and future trials

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