Current Issues in Clinical Trials

The Association of the British Pharmaceutical Industry
Current Issues in Clinical Trials

A meeting held at BMA House in London on 9 October 2003 to explore a range of issues related to clinical trials.
Meeting Objectives

The meeting aimed to involve the whole range of researchers, service user researchers, research managers, patients and patient advocacy groups and enhance the involvement of patients at all stages of research. There are a number of ethical, procedural and legal issues involved in clinical trials, many of which have been around for a number of years. But things moved on in the 80s and early 90s, with AIDS activists changing the way research was carried out and how information that came out of them was made public. The European Directive on Clinical Trials will build some of this into legislation.
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A quarter of the world’s top 100 medicines were developed in Britain, so it comes as no surprise that this country is a leader in clinical research. This country is also at the forefront of international medicines research – only the USA has discovered and developed more medicines. The largest sponsor of clinical trials in Britain is the pharmaceutical industry, although valuable medicines research is also carried out by research charities, Research Councils and the NHS.

More and more trials are conducted in centres in other countries around the world and attracting clinical trials to this country is vitally important for the NHS, for the academic world, for the economy and, above all, for patients.

Finding and developing new medicines does not come cheap. It costs about £500 million to develop a new medicine and the process is a lengthy one, taking an average of 12 years. A rigorous assessment of a new medicine’s quality, safety and efficacy is the hallmark of the clinical trials carried out in Britain and it is the aim of the pharmaceutical industry to ensure that those standards are maintained and raised yet further.

People have a right to balanced and impartial information about clinical trials and the ABPI has endorsed an initiative which gives details on the internet of current and future trials. That may help people to choose to take part in trials and so further our knowledge about the pathways and mechanisms of disease. The new medicines that may come as a result will be of benefit to everyone.

Britain has traditionally been a leader in clinical research, providing high standards of scientific research and clinical care. This booklet asks questions about what has often been a contentious issue and gives some forthright views.
Nick Partridge has worked for the Terrence Higgins Trust since 1985 and was appointed its Chief Executive in 1991. Over the past 18 years Nick has been a consistent voice in the media coverage of AIDS in all its aspects from health promotion, social care and advocacy to treatment issues.

Terrence Higgins Trust and London Lighthouse merged in October 2000 to create the UK’s leading AIDS charity. It delivers health promotion campaigns to slow the spread of HIV and offers a wide range of services to people whose lives are affected by HIV or AIDS. The Terrence Higgins Trust has negotiated mergers or service transfers with 14 other AIDS charities in the past four years and has over 600 volunteers and 220 staff.

Nick was appointed as a commissioner of the Commission for Health Improvement in November 1999. He is also Chair of INVOLVE, an advisory group promoting public involvement in NHS, public health and social care research.
Dr Pablo Fernandez is currently Senior Vice President of Clinical Research at PharmaNet, a full service contract research organisation dedicated to providing drug development services on a worldwide basis. Since joining the pharmaceutical industry in 1979, Dr Fernandez has headed International Clinical Research departments for several major pharmaceutical companies, including Lederle, Wyeth-Ayerst, the Wellcome Foundation and Bayer Biologicals. He has been intimately involved in the development of a number of medicines in oncology, immunology, infectious diseases, neurology, psychiatry and in other therapeutic areas. Dr Fernandez has developed relevant expertise through the management of multinational multicentre trials and the co-ordination of groups of patients and experts in these and other therapeutic areas, coupled with in-depth training in project management and organisational disciplines.

 Patients on trials: before

**Patient recruitment: the challenge**

- The scientific support for trials is solid and subject of constant scrutiny
- The ethical basis of volunteering has been well established
- Participation in clinical trials has been shown to be beneficial for patients
- Number of participating patients remains comparatively low
  - Published figures for certain well studied therapeutic areas show participation rates of 2-5%
  - Widely held suspicion of research aims and methods

 Patients on trials: after

- All data from a clinical trial has to be included in the analysis of results and final report
- Reports of all trials are provided to the Medicines Agency
- Trial data are presented at scientific meetings and published in journals
- Scientific scrutiny of the research methods and results
- Negative as well as positive results are often reported by the lay press
Clinical Trials

Clinical trials are an essential part of the regulatory process, assuring that data are correctly assembled in advance of the marketing authorisation of a medicine.

Once a patient has been recruited for a clinical trial, the regulatory requirements are strict and adhered to by all main countries around the world. They are set out in International Conference on Harmonisation Good Clinical Practice guidelines and the World Medical Association Declaration of Helsinki.

The ethical requirements cover:
- comprehensive and relevant information
- risk/benefit balance
- clear and intelligible language
- multicultural adaptation
- ‘thinking time’
- opportunity for patient feedback throughout the trial
- obligation to maintain the patient’s information during the trials.

There are a range of safeguards to ensure the safety of participants while the trial is being conducted:
- continuous 24-hour surveillance is mandatory
- the regulations demand real-time information
- investigators, ethics committees and government agencies are informed by the trial’s sponsors
- patients are informed of issues potentially affecting the risk/benefit balance
- new informed consent may be required to cover changes in the risk/benefit balance.

After the trial has been concluded, all data has to be included in the analysis of results and in the final report. The reports of all trials are provided to the medicines agency – the MHRA in the UK, the EMEA for the EU. Subsequently, trial data are presented at scientific meetings and published in journals, ensuring scientific scrutiny of the research methods and results. This process involves making public the negative, as well as the positive, results of the trial.

As trials are only conducted on compounds that have been shown to present desirable effects and where previous results suggest continuing development of a compound, there is a tendency for the trials to show positive results. A summary of all the information used to register a medicine in Europe is now available as a European Public Assessment Report, and a brief summary of such information is also provided in the electronic Medicines Compendium – the summary of product characteristics.
Dr Richard Tiner is the Medical Director of 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.

PROTECTION OF PARTICIPANTS

- Benefits > Risks
- Understand the details of the trial in advance
- Able to withdraw at any time
- Data protection
- Indemnity / insurance
- Contact point

ETHICS COMMITTEES

- Independent
- Responsible for protecting rights, safety and well-being of participants
- Opinion before trial begins
- Competent
- Transparent
- Legal entity
Implications of new legislation

The new European Directive on Good Clinical Practice in Clinical Trials establishes the provisions on the conduct of clinical trials on human subjects involving medicinal products. It sets out good clinical practice and internationally recognised ethical and scientific quality requirements that must be observed for designing, conducting, recording and reporting clinical trials. The Directive states that a clinical trial subject’s protection is safeguarded through risk assessment based on toxicological screening, screening by ethics committees, screening by competent authorities – the Medicines and Healthcare products Regulatory Agency in the UK – and through protection of personal data.

An important message in the preamble to the Directive is that obsolete or unnecessarily repetitive tests will not be carried out.

A new aspect as far as the UK is concerned is the introduction of legislation for a ‘single opinion’. This has created a great deal of debate around Europe. In 1997, Multicentre Research Ethics Committees (MRECs) were developed and, in clinical trials involving five or more centres, they were required to give an opinion on the science and ethics of research. Local Research Ethics Committees (LRECs) had previously given opinions and some of them were unhappy to give up this activity to MRECs. From 2004, there will be a lead ethics committee opinion to give a view of the ethics and science of a project, which will hold for wherever it is carried out in the UK.

It is clear that the Directive covers both commercial trials carried out for and by pharmaceutical companies, and non-commercial trials. It also recognises that there need to be simplified procedures, especially in the area of good manufacturing practice, again creating a lot of debate.

Good Clinical Practice inspections will be required to confirm that data have been properly generated, recorded and reported. They will have a legal basis and will become mandatory from May 2004. Information on this issue has not been published yet, but its purpose is to protect patients. Participants in clinical trials will be required to give their consent to inspectors having access to their personal information as part of an inspection.

The Directive is concerned with compliance with good clinical practice to ensure the rights, safety and well-being of participants. This is a key factor of the entire Directive.

Patients are represented and their interests protected through independent ethics committees, which will give their opinion before the clinical trial begins. The committees have to be competent in regard to both the ethics and science of the research being proposed. This will demand a mixture of expertise, including lay people, perhaps about one third. Their activities have to be transparent, for example, they will have to produce an annual report available to the public. For the first time, ethics committees will have legal status.

A cardinal point is that benefits must outweigh the risks. Participants must understand the details of the trial in advance and are able to withdraw at any time. Their personal data will be protected and they must be assured that there is indemnity or insurance should anything go wrong and compensation be necessary. They must be provided with an independent contact point – someone with whom they can discuss problems or issues about the trial.

The Directive requires that from May 2004, all clinical trials will have to have a sponsor. This will not be a problem where commercial trials are concerned, but public trials are a different matter. It is not certain that all NHS Trusts and universities have taken this on board yet. Pharmaceutical companies supporting investigator-led studies should consider if they might sponsor such trials, because any trials without a sponsor on 1 May 2004 will not legally be allowed to continue. Patients will suffer if that happens.

The current situation in the UK is that after about 160 very detailed responses to the consultation exercise, completed in May 2003, final UK legislation is expected in February 2004. One big element in the delay in completion is that the Commission has still not published its supporting Directive on Good Clinical Practice.

The Council of Europe’s Commissioner for Human Rights said on 11 September 2003: “The main objective of the regulation of research with human beings is the protection of the safety of the subjects, prior to the interest of science and society. It is important to resist the pressure of the market in this field.”

A new ABPI web site has started to publish details of all UK clinical trials sponsored by pharmaceutical companies. There are currently nearly 90 clinical trials on the Clinical Trial Register from six companies that are making information about their trials public, including some prospective studies, especially in the field of cancer. The web site address is https://www.cmrinteract.com/clintrial.

Dr Susan Griffith joined the pharmaceutical Industry in 1987, and since this time has held a variety of different positions in four different companies, most of which relating to international drug development. In her role as the Medical Director for the UK and Republic of Ireland, she has been responsible for all medical activities in these countries, including an extensive clinical trial programme involving a broad range of products in various stages of development.

Dr Susan Griffith, Medical Director  
Eli Lilly & Company

Pragmatic Clinical Trials

In 1958, the World Health Organisation defined health as not merely the absence of disease, but also the complete physical, psychological and social well being [of the individual]. This is a good starting point for pragmatic clinical trials, as it embodies a more holistic view of health.

The conclusions drawn from clinical trials relate to the overall findings for a group of patients, but it is important to remember that each individual’s condition is unique to them. The primary aim should be to achieve optimal treatment or management of their condition.

This is an era of evidence-based medicine, but we do not know all the questions we should be asking, let alone the answers, and the issue remains of finding the optimal outcome for the individual patient.

Pragmatic Clinical Trials - reflecting the real world
At Eli Lilly, information is collected in a variety of ways. Pragmatic or observational studies are different from randomised clinical trials. Randomised clinical trials (RCTs) are geared towards achieving marketing authorisation of a potential medicine and therefore need to follow strict regulatory guidelines.

RCTs aim to determine the risk/benefit of a medicine, its safety and tolerability, its optimal dose and dosing schedule, its pharmacokinetics, and makes measurements against validated and objective end points according to a predetermined study hypothesis. RCTs have a high internal validity and researchers try to ensure that there is no bias. This is done in a controlled environment, involving intensive monitoring of efficacy and safety. Companies will use established and trusted research sites, such as hospitals and GP practices with good standards of clinical care.

But RCTs are conducted in an artificial setting, with a homogeneous group of patients with limited inclusion criteria. With pragmatic clinical trials, the important concept is one of effectiveness, to see how the treatment actually works in real-world circumstances, where, for example, the treatment may not be used strictly according to its label, but according to what the physician feels is appropriate for the individual patient. Both types of study play their role in understanding a treatment.

Pragmatic clinical trials are large-scale multicentre studies in which interventions or medical policies are compared in a realistic setting. Conclusions are drawn from these studies that can be adopted directly into medical practice. They do not just have to be about drugs. The therapeutic characteristics of the treatment are evaluated within the context of the complex interactions of patient, physician and health care systems. They are therefore designed to answer policy or clinical management questions.

The advantages of pragmatic clinical trials are: a less restrictive patient population, patient-centred outcomes, and studies that include social functioning. The follow up of the patient tends to be longer and the findings can be better generalised to other patients.

There are disadvantages too, especially in the fields of selection bias - physicians will tend to select those patients that they think will come back and will tend to reject those that they think will be non-compliant. There is also the physician’s freedom to select treatments, perhaps where there is a new one and previous treatments have not worked. There are quite a few pragmatic clinical trials being carried out by organisations other than the pharmaceutical companies.

Eli Lilly has 14 pragmatic clinical trials in progress in all the areas where the company has therapeutic interests, and in quite different areas. This means that the study designs are very different, that they are carried out in primary and secondary care situations, are conducted before and after product launch and may not always involve an Eli Lilly product. Pragmatic clinical trials are easier to recruit for in other EU countries than in the UK.

Setting up pragmatic clinical trials has been a learning process. Previously, researchers looked at a therapeutic area and a drug. Now the whole health care pathway has to be considered, as well as what matters to the patient.

Pragmatic clinical trials are large - Eli Lilly has one with 110 sites. The company needs to approach a large number of doctors, many of whom are not known to the company. This is addressed through mailshots, screening and visits, but has workload implications for physicians who have limited time. The trials are carefully reviewed by MRECs and LRECs at the same level of review as for RCTs. Trusts and PCTs also review the trials.

Dr Griffith gave, as an example, details of SOHO, a pan-European prospective observational study of health outcomes associated with antipsychotic medication therapy for outpatients treated for schizophrenia. SOHO looks at costs and outcomes, as well as pharmacological treatment patterns for olanzapine compared to other antipsychotics. The trial has 10,800 patients in 10 different countries, involving 1,100 physicians and a three-year follow-up.

The art of pragmatic studies is to capture the best quality information possible. Observational studies can provide data on outcomes relevant to patients, but also support in achieving NSF targets, such as (in schizophrenia) reduction in suicide rates, hospital admissions and controlling crime and violence. These are aspects that would not be asked for in a randomised clinical trial.
After qualifying in medicine in the mid 1960s, Iain Chalmers practised as a clinician for seven years in the UK and the Gaza Strip. In the mid 1970s, after further training at the London School of Hygiene and Tropical Medicine and the London School of Economics, he became a full-time health services researcher, with a particular interest in assessing the effects of healthcare. He directed the National Perinatal Epidemiology Unit between 1978 and 1992, and the UK Cochrane Centre between 1992 and 2002. His main current interests are the history of the development of methods to test the effects of medical treatments, and promoting public understanding of these methods. He is Editor of The James Lind Library (www.jameslindlibrary.org), which documents the evolution of fair tests of medical treatments.

What do I want, as a patient?

When there are uncertainties about the relative merits of my treatment options, I want to be invited to participate in any ongoing, rigorous and relevant randomized controlled trials for which I may be eligible.
Talking from a patient’s point of view

Sir Iain said that he proposed to talk from a patient’s point of view about what he wanted from clinical trials. When there are uncertainties about the relative merits of treatment options, he wanted to be invited to participate in any ongoing, rigorous and relevant randomised controlled trials for which he might be eligible. This is not out of altruism but, knowing the evidence, he knows that he can look after his interests in this way.

To whom should he look to promote and protect his interests as a potential participant – to research funders, researchers themselves, or research ethicists? As far as research funders and researchers are concerned, there are too many perverse incentives, primarily money, that lead to clinical trials of no relevance at all to patients. It is the responsibility of companies to look after their corporate interests, but the question is the degree to which others need to be dragged into that agenda. But there are also problems within the academic world itself, such as competition which limits collaboration, and a competitive environment which can lead to short-term, trivial studies done to decorate curricula vitae.

Research ethicists have been scrutinised less than they ought to have been. They have failed to expose and confront some of the perverse incentives for research, to require that proposals for new studies are informed by systematic reviews of relevant existing evidence, and to insist that the results of all clinical trials are made publicly available. Failure to publish is breaking an implied contract with those taking part in the trial, who believe that they are contributing to a growth in knowledge. Knowledge cannot grow if the results of clinical trials do not see the light of day.

The consequences of not addressing these issues leads to poor research. We need less research, better research, and research done for the right reasons. So the question remains: if research funders, researchers and research ethicists cannot be relied upon to protect the best interests of patients, who can be? What should be done to ensure support for RCTs addressing questions that are of no interest to industry, but of great importance to patients?

Non-commercial controlled trials have a long history in this country, beginning with James Lind’s controlled comparison of different treatments for scurvy, reported exactly 250 years ago, and including the exceptionally important UK-led Antiplatelet Trialists Collaboration’s analyses of the effects of aspirin on cardiovascular disease. But there is now a marked and worrying decline in the number of non-commercial trials being carried out in the UK.

Where do patients find out about clinical trials that are relevant to them? They could try their GP, NHS Direct or the National electronic Library for Health, but information is hard to come by. Some information is available in the field of cancer and other fields through the website www.controlled-trials.com. But there has not been nearly enough progress and there is not nearly enough information about ongoing trials.

Commentaries on clinical trials registered at such sites and accessed through the NeLH could cover the importance of the questions being addressed by the trial and whether these questions had already been satisfactorily answered in previous research. They should also indicate whether the design of the trials is scientifically and ethically robust, whether the primary outcomes being studied include those that matter to patients, and whether there are arrangements for communicating the results of the research to the participants.

All these issues could be addressed in a patient-led Good Controlled Trials Guide. A scoping study was commissioned for Consumers in NHS Research (now INVOLVE) which found that there is widespread support for the concept of publicly available information on randomised clinical trials.

But there is not much sign of serious action being taken. The public and patients should insist on the application of principles of good scientific and ethical practice. They should insist that all new research studies be designed in the light of systematic reviews of relevant existing research evidence. They should insist that details of all clinical trials be registered publicly at their inception and that the eventual results should be made public.

There can be no acceptable progress without an increase in:
- public knowledge about clinical trials
- public anger about the status quo
- public pressure for change
- public involvement in all phases of clinical trials.

Sir Iain was also worried about how his interests as a patient will be protected and promoted. Unfortunately, he felt that he can no longer depend on some patient organisations, feeling that they can no longer be relied on to promote the interests of the constituencies that they purport to represent in a completely impartial way.
Robert Meadowcroft joined the Parkinson’s Disease Society in November 1999 as Director of Policy, Research and Information, having worked with RNIB and Scope. The Society is taking forward a new research strategy and also now involves people living with Parkinson’s disease in the work of its Research Advisory Panel. He has worked with a broad coalition of organisations to secure changes to UK legislation in order that embryonic stem cell research can take place in the UK and now to resist restrictions being considered in the EU. He is currently a Vice Chair of the Neurological Alliance – which represents more than 50 organisations – and has also contributed to a Working Party looking to develop the National Service Framework on Long Term Conditions. Robert has also had many opportunities to speak on behalf of the Society in the media and to press the research and policy priorities that will make a difference in Parkinson’s disease and related fields.

Information is needed

- To be aware of opportunities
- To know what is involved
- To be able to discuss all aspects
- To be open about the possible benefits
- To know how to report any side effects
- How to get involved

Clinical trials

- Parkinson’s is a specific condition and people are motivated and keen to take part
- Common concerns re quality of life issues
- Anxious to get better treatment
- Also, keen to help others
- Do you have similar objectives?
Patients and protocol

The Parkinson’s Disease Society was founded in 1969 by a carer. There are 120,000 people with Parkinson’s in the UK, and the Society has some 28,500 members and more than 300 branches and support groups. The Society has three principal objects – to support research into the cause, cure and treatment of Parkinson’s, more information for people with the condition and those caring for them, and finally, welfare and support. Its aim is to be one of the leading neurological charities in the UK, serving all people with Parkinson’s.

Research is important for the Society. It supports breadth and quality of research. It is not just led by projects of interest to the research community – it is able to identify gaps and commission research. It also aims to improve the dissemination of research and there is a Research Advisory Panel drawing on expertise from researchers and members.

As far as clinical trials are concerned, Parkinson’s is a specific condition and people are motivated and keen to take part. People commonly have concerns about quality of life issues and are anxious to get better treatment. Participants are keen to help others and want to know if the aims of those carrying out the trial and the participants are shared.

One reason that participation in trials is low is that people do not have the information on how to get involved. People who are interested in taking part should:
- be aware of the opportunities
- know what is involved
- be able to discuss all aspects of the research
- be open-minded about the possible benefits
- know how to report any side-effects
- understand how to get involved.

The Society occasionally has to give advice to people who are desperate to take part in clinical trials before the trials are properly set up, because they are seeking improvements in treatment for themselves or others.

A lack of feedback to participants about trials is a frequent issue – they want to know what the end date is, where the results will be published, what the outcomes were, etc. Expert patients who are better informed and more confident about their treatment are more likely to benefit from it. People need to be more aware of the process and of the importance of clinical trials. That will mean that they will have more questions for those who design the trials, but that is a welcome development. In summary, there is a need for more and better information and genuine consultation.
Discussion

During the discussions which followed the presentations, a number of points were discussed. What follows is a summary only – not all the questions raised were answered by a single member of the panel.

**Should patients be involved in the design of clinical studies?**

Patient involvement helps to accelerate advances and there is real respect for the opinion of patient groups. Patients are important in the prioritisation of key elements of clinical trials at the earliest stages.

**What are the issues around informed consent?**

It has been standard practice for years that there is a requirement for participants to be fully informed about what their trials imply. The European Directive brings this into the legal framework. Fraudulent activity in regard to consent is the most common cause found in investigations of serious research misconduct.

**As concerns about safety issues may affect decisions on whether to go ahead with a study, should there be an option of a disclaimer that participants could sign, to limit the legal liability of the researchers?**

This raises serious ethical issues and needs very careful thought. Although the idea has some merit, the foremost consideration when a trial is being conducted is not to cause harm. Individuals may claim inclusion as a right, but anarchy is not the answer either. While it is clear that patients do better in clinical trials, there are risks too – it might not always be best to be a treatment pioneer. A study published in the *Lancet* described four focus groups of physicians, GPs, rheumatologists and patients invited to consider their different priorities. All agreed that they wanted fewer drug trials, but better surgical techniques and education programmes. Researchers’ agendas do not always overlap with those of other interest groups.
What will be the impact of the European Directive on Phase 1 trials?

For the first time, Phase 1 studies will be brought into regulation. Until now, all that was necessary was an Ethics Committee approval. The MHRA has agreed that approval will be quick (14-21 days) and that it can be done in parallel with an ethics committee opinion. This is important, because the UK does 50 per cent of Phase 1 studies in Europe and that level needs to be maintained.

Should pregnant women be excluded from pragmatic clinical trials?

A trial’s first obligation is safety. Whether to go ‘off label’ is a decision for the physician. Pragmatic trials are ‘real-life’ situations and it is important to collect information in all situations where a medicine is used.

Should incapacitated people be involved in clinical trials?

The European Directive will not prevent research with incapacitated people, including use of potential treatments in emergency situations. It is important that an independent representative is available. For people with longer-term incapacities, ethicists must consider more carefully whether they do in fact occupy higher moral ground than others, and whether they may be preventing useful and ethical research.
Discussion

What incentive is there to enter a trial if the results are likely to show positive outcomes and that the benefits outweigh the risks anyway? Surely, the basis of randomisation is uncertainty.

Trials are in general good for patients, but that does not prejudge the superiority of the medicine being studied over the comparator treatment. However, for all clinical trials, there will be prior information about the medicine which will indicate whether the likely benefits will outweigh the risks of taking part. Products in the later stages of development may have already proved themselves to an extent. What the companies are looking for in Phase 3 trials is for an increased level of information on safety and efficacy, as the result of smaller trials unconfirmed by larger ones may constitute an unreliable basis to grant an authorisation. Sometimes, new safety and efficacy information emerges even at the Phase 3 stage.

Why might a pharmaceutical company not want to publish trial results?

Sometimes trial results are negative or equivocal and in those situations some companies might wish to delay publication or not publish at all. Furthermore, peer-reviewed journals are often not interested in such trials, but with the increase in electronic publishing, publication of all trials is now quite possible. Pharmaceutical companies must by law look after the interests of their shareholders and sometimes it might not be seen to be in the interests of the shareholders to publish until some time later, if at all. But the big question is whether the public is prepared to tolerate that. If a patient is told up front that the results will not necessarily be published, that is acceptable, but most participants believe that they are contributing to the growth of knowledge and not publishing is a betrayal of that trust.

The Directive talks about reporting, and the pharmaceutical industry’s Model Clinical Trial Agreement between the industry and NHS Trusts and PCTs contains a section on publication. If a company does not publish ‘in good time’, the investigator has the right to publish whether the company agrees or not. The key is to get the information back to the patients, but although companies can inform doctors about the drugs concerned, the patients’ details are anonymised. Only the doctors can know which of their patients participated in a trial and therefore only the doctor can pass on relevant information to the patients.
How can we increase representation of patient expert members on MRECs to encourage requests for information?

The answer to this is to make companies’ activities much more open. All trials should be publicly registered. The ABPI is encouraging its members to be more open: the Clinical Trials Register web site
https://www.cmrinteract.com/clintrial is a start and includes details of prospective as well as retrospective studies. There are also guidelines for advertising for patients to take part in trials. Hamish Cameron’s initial good work on publication some years ago is now reflected in the guidelines on Good Publishing Practice www.gpp-guidelines.org developed by Liz Wagner and her colleagues in industry. It should serve as a guide and would make companies’ agendas clearer.

The aim is for a third of members on ethics committees to be people with expertise outside the medical and scientific communities. If Eli Lilly funds research, for example, it is a condition that the results will be published – there is no point in doing studies if the results do not see the light of day. A problem can arise where a potential medicine is dropped because it did not work in a large enough population, although it did work for a few, as hopes may be raised too much.

How can patient groups help in disseminating information from and about clinical trials?

This depends on the size and resources of the patient group concerned. The Parkinson’s Disease Society has an established page on research in its magazine and is exploring possibilities through its web site. It also has contact through its local branches. Patient groups should insist that information about all new research should include details of existing research, wherever it is being carried out. All details of any clinical trial should be publicly registered at its inception and all results should be published.
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.

**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:

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.
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 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.
Useful information

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