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 fully 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 Association of the
British Pharmaceutical Industry
12 Whitehall, London SW1A 2DY
Telephone: +44 (0)20 7930 3477
Fax: +44 (0)20 7747 1411
E-mail: abpi@abpi.org.uk
Website: www.abpi.org.uk

ABPI Scotland
9 Queen Street, Edinburgh EH2 1JQ
Telephone: 0131 247 3688
Fax: 0131 225 4865

ABPI Cymru Wales
Floor 4, Caspian Point 2, Pierhead Street,
Cardiff Bay, Cardiff CF10 4DQ
Telephone: 02920 454297
Fax: 02920 454298

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.

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.

THE BENEFITS OF CLINICAL RESEARCH TO 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.

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.

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 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.

BSC Print 4k Oct 03