UK CLINICAL RESEARCH COLLABORATION

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Understanding Clinical Trials

The UK Clinical Research Collaboration (UKCRC) is a partnership of organisations working to establish the UK as a world leader in clinical research, by harnessing the power of the NHS. The aim is to revitalise the environment for clinical research in the UK, benefiting patients and the public by improving national health and increasing national wealth.

The partnership includes the main UK research funding organisations, academia, the NHS, regulators, industry and patients.

One of the key aims of the partnership is to increase public awareness and understanding of clinical research and to promote active patient and public involvement in the research process.

www.ukcrc.org

The UKCRC welcomes any feedback that can help to improve our publications. If you would like to make any comments on this booklet please contact the UKCRC by email at info@ukcrc.org or in writing to:

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Understanding Clinical Trials

1st edition

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Introduction

If you are being treated in the NHS you may be asked to take part in a clinical trial. Clinical trials are research studies that involve patients or healthy people and are designed to test new treatments.

In this booklet we use the term 'treatments' to mean a wide range of health care approaches that can be tested in a clinical trial including drugs, vaccines, other approaches to disease prevention, surgery, radiotherapy, physical and psychological therapies, educational programmes and methods of diagnosing disease.

This booklet has been written to try to answer the many questions people ask about clinical trials. It explains what clinical trials are and why and how they are carried out. It is designed to give you the information to help you to decide whether to take part in a trial. It also includes some of the questions you may want to ask before you make a decision to join a trial.

What are clinical trials?

Clinical trials are medical research studies involving people. They aim to test whether different treatments are safe and how well they work. Some trials involve healthy members of the public. Others involve patients who may be offered the option of taking part in a trial during their care and treatment. Clinical trials are carried out to try to answer specific questions about health and illness.

They aim to find the best ways to:

- prevent disease and reduce the number of people who become ill
- treat illness to improve survival or increase the number of people cured
- improve the quality of life for people living with illness, including reducing symptoms of disease or the side effects of other treatments, such as cancer chemotherapy
- diagnose diseases and health problems.

Clinical trials cover a broad range of different types of research. For example, trials are often used to test new medicines or vaccines but can also be used to look at new combinations of existing medicines. They can also be used to test whether giving a treatment in a different way will make it more effective or reduce any side effects. Some trials are designed to try out ways to prevent a particular disease in people who have never had the disease, or to prevent a disease from returning. The

treatments being tested in these types of studies can include vaccines, but may also involve drugs or dietary supplements such as vitamins and minerals.

Clinical trials are not always about testing medicines, they can be used to test 'interventions' aimed at modifying a person's behaviour or lifestyle. This could include an educational programme designed to improve a person's understanding of their medical condition and help them to manage it more effectively, or a psychological treatment, such as the use of cognitive behavioural therapy for the treatment of anxiety or depression.

Why are clinical trials important?

Clinical trials are the best way to compare different approaches to preventing and treating illness and health problems. Health professionals and patients need the evidence from trials to know which treatments work best. Without trials, there is a risk that people could be given treatments which have no advantage, waste resources and might even be harmful. Many treatments that are now in common use in health care were tested in clinical trials.

Some types of clinical trial are designed to look at a treatment at an early stage of its development. Researchers and regulators will look at the information they have gathered and decide whether it is safe and appropriate to continue the development of that treatment. If the treatment has no benefit or has serious

side effects, it may not be developed further.

During the later stages of development of a treatment researchers will report on the benefits and risks so that doctors can decide whether or how best to use it. It is important that the results of clinical trials are published so that others can use the information to help them make decisions about treatment and health care. Clinical trial results also form an important part of the evidence used to decide whether a particular treatment will be provided through the NHS.

How are trials set up?

Clinical trials are designed by doctors and other specialists with input from a wide variety of people, increasingly including patients. They work together to decide what questions need to be answered. First of all they look carefully at the results of the trials that have already been done to find out what is already known. This is called a **systematic review**. A systematic review provides more accurate answers than individual trials and also helps to identify important questions that still need to be answered through further research.

Doctors, nurses, patients and researchers work together with statisticians, trial managers and representatives from pharmaceutical companies if relevant, to design the best possible trial. The design for the trial forms the basis of the **trial protocol**.

When the trial protocol is ready it is sent to a **research ethics committee**, an independent group of people that includes doctors, nurses, other medical staff, members of the public and sometimes lawyers. They decide whether the trial is ethical. In particular they check whether:

- the potential benefits of a new treatment are likely to outweigh the side effects
- the information provided to help people to decide whether they want to participate in a trial is clear and satisfactory
- the way in which people will be asked to take part in a trial (recruited) is appropriate
- there will be compensation for people in the trial in the unlikely event that something goes wrong
- travel expenses will be offered to people who take part.

The trial can only go ahead when it has been approved by an ethics committee.

Who can take part in clinical trials?

All trials have guidelines about who can take part. These are called **eligibility criteria**. Eligibility criteria are used to ensure that trials include the sort of people who may benefit from the treatment, and to make sure that people who take part are not exposed to avoidable risks. This means that there may not

always be an appropriate or suitable clinical trial for you to take part in.

The **inclusion criteria** help the researchers to decide who *can* take part in the trial. Some trials only include people in a certain age group, or of one sex, or at a particular stage of their illness.

The **exclusion criteria** state who *cannot* take part in the trial. For example, many drug trials do not allow pregnant women to take part as there may be a risk to the unborn baby. People who are already taking particular medicines may also be excluded as these may affect the trial treatment.

Before you go into a trial you may have to have some extra tests to see if you are eligible or to ensure that you are not likely to be at risk of being harmed by the treatments in the trial. For example, if a potential side effect of a new drug is that it increases blood pressure you may have your blood pressure checked to see if you are eligible to join the trial.

How are people recruited to a trial?

A clinical trial is often run in a number of different hospitals or health centres. The doctor or nurse who asks you to take part in a clinical trial may not be the person who designed and set up the study, especially if it is very large. However, they will have been fully briefed about the study before agreeing to become

involved. They can give you all the information you need and will be able to answer your questions.

What are the risks and benefits of trials?

Clinical trials are carefully designed to minimise the risks and maximise the benefits to all who take part, whatever treatment they receive. Some trials will have very little risk involved. However, the risks of a trial may be greater when less is known about the treatment being tested. Before any drugs are first given to people, they will have been developed in a laboratory and checked for safety in animals.

In all trials the treatment may cause side effects that doctors cannot predict and that you may not be expecting. These may be unpleasant and very rarely can be life-threatening. You should be told everything that the researchers know about any possible risks and side effects and why the trial is necessary so that you can make an informed choice about whether to take part.

If you take part in a trial you will be monitored regularly during and after the study. You will have regular tests and you may be asked some extra questions about how you are feeling. You may also be asked to fill out questionnaires or to keep a diary. Sometimes this means going to your hospital or GP more often than you would normally, so bear this in mind before you agree to take part. Ask how many extra visits will be needed and

consider how convenient this will be for you. Usually there will be money available to help with any extra costs you have.

The benefit to you of this extra attention is that any changes in your health, whether or not they are related to the treatment you are having, are frequently picked up and acted upon earlier than if you were not in a trial. However, some people find that the extra attention makes them worry more about their condition and prevents them from 'getting on with their life'.

It is important to remember that not everyone receives a new treatment in a clinical trial. A clinical trial needs to compare a new treatment with the standard treatment already in use, if there is one. Some people in a trial will therefore receive the standard treatment but, until the results of the trial are analysed, no one will know which treatment is better. **'New'** does not always mean **'better'** and you may not be worse off if you do not receive a new treatment.

People who take part in trials often feel that they are taking an active part in their health care. They are also helping others, and possibly themselves, by helping to identify the best treatments.

How are trials supported?

Many different types of organisation support clinical trials. These include:

- the **NHS**
- the **Medical Research Council** and government departments or agencies
- **charities**
- **pharmaceutical companies**.

All trials, no matter who funds them, are checked and monitored in similar ways to make sure that the people who take part are protected. Each trial also has a **sponsor** who is responsible for the conduct of the trial. The sponsor may be the organisation funding the trial or the institution hosting the research, for example, a university.

Many of these organisations involve patients to help decide what will be researched in the future. It is essential that research takes into account the needs and interests of the people it is trying to help. Specialists are often aware of gaps in knowledge about diagnosis and treatment but patients and their families may also see aspects of care that need further research.

How are trials designed and run?

Are there different types of trial?

Clinical trials are carried out in a number of stages. Early stage trials usually involve a small number of patients or healthy people. When psychological treatments or educational programmes are being tested, these early stage studies can be used to 'fine tune' the treatment before it is tested in a large group of people. For trials of medicines and other treatments, early stage studies are carried out in a small group of people to assess safety by looking for unwanted side effects. Later stage clinical trials usually involve larger numbers of participants and are usually **randomised trials**. The process of **randomisation** is explained later in this section.

A good example of how the clinical trial process helps to answer important questions is the development of new drugs. These are first developed in the laboratory to see whether they may be helpful in the prevention or treatment of a particular illness. They are then tested in animals to check their safety and to find out how they affect the body. If they look like they may be of benefit and are likely to be acceptably safe they will then be tested through different stages of clinical trials. For drugs, the different stages of clinical trials are known as **phases**:

Early stage:

Phase 1

Phase 1 is the first stage and usually involves small groups of healthy people or sometimes patients. Phase 1 trials are mainly aimed at finding out how safe a drug is.

Phase 2

By the time a drug reaches Phase 2, researchers will know quite a lot about it.

Phase 2 trials aim to:

- test the new drug in a larger group of people to better measure the safety and side effects
- see if the drug has a positive effect in patients.

Later stage:

Phase 3

Phase 3 trials are large and may include hundreds, or sometimes many thousands, of patients from all over the UK, and often from several countries.

Phase 3 trials aim to:

- compare the effects of newer drugs with the standard treatment, if there is one
- find out how well the drug works and how long the effects last
- find out more about how common and serious any side effects or risks are and about any possible longer term problems that could develop.

Phase 4

Phase 4 trials are carried out after a new drug has been shown to work and has been given a licence.

Phase 4 trials aim to find out:

- how well the drug works when it is used more widely
- the long-term risks and benefits
- more about the possible rare side effects.

Phase 1 trials only pick up very common side effects. Phase 2 trials help to pick up less common side effects, but Phase 3 or 4 trials are needed to properly assess safety and risks.

If you are asked to take part in a trial, there are a number of terms which you may hear:

Controlled trials

Controlled trials are designed to compare different treatments. Most controlled trials compare a new treatment with the standard or usual treatment by setting up two groups of people. One group, known as the **trial group** or **intervention group**, are given the new treatment. The other group is given the standard treatment and is known as the **control group**. In situations where there is no standard treatment the control group may not be given any treatment at all or may be given a **placebo**.

A **placebo** treatment is designed to appear very similar to the treatment being tested. For example, in a drug trial the placebo looks exactly like the real drug, but in fact it is inactive. By comparing people's responses to the placebo and to the treatment being tested, researchers can tell whether the treatment is having any real benefit.

The control group is very important. Comparing the results of the control group with those of the treatment group is the only way researchers can reliably find out whether any improvement seen with the new treatment is really due to that treatment and not just due to chance.

Blind trials

In a **blind trial**, the participants are not told which group they are in. This is because if they knew which treatment they were getting, it might influence how they felt or how they reported their symptoms. Some trials are **double-blind**, which means that neither the participants nor the doctors treating them know which people are getting which treatments. This also avoids the doctors' hopes and expectations influencing the results of the trial.

To prevent people from guessing which treatment they are getting, all the treatments are made to look as similar as possible. For example, in a drug trial all the tablets will look the same whether they are the new treatment or the standard treatment.

Randomisation

Many trials are **randomised**. This means that people are allocated at random to the treatment groups in the trial, usually by using a computer programme. This is done so that each group has a similar mix of people of different ages, sex and state of health.

If it were left to the doctor or patient to decide who should get which treatment they might be influenced by what they know about their illness. Patients who are more or less likely to respond to a new treatment might all go into one particular group. In that situation, if one group did better that the other it would not be clear whether the difference was due to the treatment or because the groups were different.

If the people are allocated to the treatment groups at random, like will be compared with like. If one group does better than the other, it is likely to be because of the treatment, as the two groups are very similar in every other way.

Why do some trials need many people?

Some clinical trials need thousands of people to take part. This is because sometimes the difference between the effects of two treatments is small. Therefore large numbers of people are needed to find out reliably whether one treatment is better than another. Statisticians give expert guidance to help the researchers make sure a trial includes enough people to give reliable results.

Why do trials sometimes take many years?

It can sometimes take a long time to get the results of particular trials. This can be for a number of reasons:

- it can take a long time to recruit enough people to take part in the trial
- it may involve giving a treatment over a long period of time
- it may be important to follow up patients over a long period of time to get a reliable picture of the long-term effects of a treatment.

What is 'informed consent'?

A doctor, nurse or other researcher should always ask your permission to enter you into a clinical trial. They cannot enter you into the trial if you do not give your consent.

There are a few exceptional circumstances where the consent process is different, and people might be entered into a trial without their consent. For example, in a trial of the treatment of head injuries or dementia an individual may not be able to give their consent. In these cases consent may be obtained from a relative or other legal representative and there will be additional safeguards to protect the participants.

Where clinical trials involve children the consent process is also different and will be fully explained by the person recruiting to the trial.

To help you decide whether you want to take part in a trial, the researcher should explain:

- the aim of the study - what it is trying to find out
- how you will be treated and what you will need to do
- what the possible risks and benefits are.

It is important that you are satisfied that you have enough information to make a decision and to give your **informed consent**. You should feel free to ask any questions that are

important to you in helping you to reach a decision. You should also feel satisfied that you have been given enough time to think about the trial and what it will mean to you.

The person inviting you to take part in the trial should first discuss the study with you and answer your immediate questions. They should also give you an information leaflet about the trial that you can take away and read in your own time. You may want to discuss it with your family or friends and consider any practical issues, such as extra appointments and tests.

If you decide that you do want to take part you will be asked to sign a form that says that you agree to join the trial and that you have decided to do so of your own free will. You will be given a copy of the signed consent form to keep. If English is not your first language, the trial should be explained to you in your preferred language. You should also be given a consent form that has been written in your preferred language.

The process of informed consent should continue throughout the trial. The researchers should continue to give you information and answer your questions. They should let you know if any new relevant information comes up during the trial so that you can re-think your decision, and withdraw if you want to.

If you decide not to take part in the trial your decision will be respected and you do not have to give a reason. You will continue to receive the appropriate medical treatment that any other person would receive. Remember that even after you have given your consent you can leave the trial at any time without giving a reason.

What happens during a trial?

As well as carrying out tests to find out how well a treatment is working, researchers will also look out for any side effects and you may be asked questions about any new symptoms you have.

Researchers will also look at the wider effects of a treatment on your life as a whole, not just its effects on symptoms. There are also detailed tests and questionnaires that are used to measure people's 'quality of life' so you may be asked:

- if you are able to take part in your usual day-to-day activities
- if you need any extra help around the home or to look after your family
- if you feel happy or sad, anxious or depressed.

Some clinical trials will also look at the cost-effectiveness of treatments and their effects on other aspects of care, so you may also be asked about how the treatment affects other areas of your life such as:

- whether you are able to work during the treatment
- the number of times you visit your doctor and nurse
- travel.

What happens at the end of a trial?

Some trials can run for many years so it may be some time before the results of a trial are known. At the end of a trial the results will be made available to everyone who took part if they want them. They will also be published so that others can use the information to help them make decisions about treatment and health care. The researchers have a duty to publish the results, regardless of what they show, and also show how the results add to available knowledge.

If you are having a new treatment as part of a trial you may not always be able to continue on this treatment when the trial ends. It may be some time before a new treatment is provided by the NHS. In this case you will be given the standard treatment. In some circumstances you may be able to buy the new treatment.

Will my information be confidential?

If you agree to take part in a clinical trial, all your trial records and any information that is collected about you will be kept confidential, in the same way as your medical records. The researchers cannot tell anyone that you are in the trial without asking you first. If your doctor or consultant is not the person who recruited you onto the trial, it can be helpful for them to be told you are in a trial as they will be responsible for your day-to-day health care; but they can only be told with your permission.

Once the trial has finished the results are usually published and often presented at conferences. No name or any information that can identify you will be used in any reports about the trial.

What happens if something goes wrong?

Before any trial can start, arrangements have to be put in place in case something goes wrong and people are harmed. Research ethics committees can refuse approval for trials where there is no insurance or other provision for compensation.

Pharmaceutical companies are insured so that if a patient is damaged by their drug, compensation can be paid. However, it is rare for patients to be seriously harmed by trial treatments, although some may cause unpleasant side effects.

Trials funded by other organisations may not have this kind of insurance, but a payment may be made if something does go wrong. Individual NHS trusts are responsible for insuring themselves against damage caused by their own studies.

Before giving your consent to take part in a clinical trial you may want to find out exactly what arrangements have been made for compensation.

How can I find out about trials that are happening now?

It can be difficult to find a suitable trial to take part in. There are a number of registers of different trials or organisations that can help you, and some of these are listed at the end of this booklet. If you would like to take part in a clinical trial but have not been asked, you should discuss it with your doctor or nurse as they will normally need to refer you. They may also know of a trial that would be suitable for you.

It is important to remember that there may not be a trial which is suitable for you.

What should I ask before I join a trial?

These are some of the questions you may like to ask before deciding whether to take part in a clinical trial.

Some general questions:

- What is the aim of the trial and how will it help people?

- Who is funding the trial?

- What treatment will I get if I don't take part in the trial?

- How long is the trial expected to last and how long will I have to take part?

- How long will it be before the results of the trial are known?

- What will happen if I stop the trial treatment or leave the trial before it ends?

Some practical questions:

- How much of my time will be needed?

- What extra tests or appointments will I have?

- Will I need to take time off work?

- Will I need extra help from family and friends?

- Will you cover the costs of my travel to take part in the trial?

- If the trial is testing a drug, will I have to collect it from the hospital, will it be sent to me by post or will I get it through my doctor?

- Will I have to fill in questionnaires or keep a diary?

- What are the possible side effects of my treatment?

- How may the treatment affect me physically and emotionally?

- Who can I contact if I have a problem? Will someone be available 24 hours a day?

- How do I find out the results at the end of the trial?

Where can I find more information?

Links

Information from the NHS about clinical trials:
http://www.library.nhs.uk/trials

MRC Clinical Trials Unit:
http://www.ctu.mrc.ac.uk/TrialInfo.asp

Searchable database of ongoing and completed clinical trials in the UK:
http://www.controlled-trials.com/mrct

UK Clinical Trials Gateway:
http://www.controlled-trials.com/ukctr

Directory of pharmaceutical industry-funded clinical trials:
http://www.ifpma.org/clinicaltrials

The U.S. National Institutes of Health ClinicalTrials.gov:
http://www.clinicaltrials.gov

Opportunities for public involvement in clinical research:
http://www.peopleinresearch.org

Organisations

UK Clinical Research Collaboration:
http://www.ukcrc.org
The UKCRC is a partnership of organisations working to transform the environment for clinical research in the UK. Raising public awareness and understanding of clinical research and increasing patient and public involvement in clinical research is an important aim of the UKCRC Partners.

UK Clinical Research Network:
http://www.ukcrn.org.uk
The UK Clinical Research Network (UKCRN) supports clinical research and helps to deliver clinical trials and other well-designed studies across the UK. Topic specific, comprehensive and primary care research networks are being funded by the UK Health Departments to support high quality research in all areas of disease and clinical need. As part of the UK Clinical Research Collaboration, the UKCRN is working towards the development of a world class infrastructure to support clinical research in the UK.

Medical Research Council:
http://www.mrc.ac.uk
For over 50 years the Medical Research Council (MRC) has been conducting clinical trials to address important public health questions and improve clinical care. MRC trials evaluate options across the entire spectrum of healthcare including; diagnostic screening, assessment of new versus existing treatments, the impact of lifestyle advice to change behaviour and prevent disease, the management of long-term conditions and rehabilitation. Many of these studies also help us understand how the body's processes work to influence health.

National Institute for Health Research:
http://www.nihr.ac.uk
The National Institute for Health Research manages and maintains health research in the NHS in England. Its work focuses on meeting the needs of the research community, patients and the public as it delivers the Government's health research strategy, 'Best Research for Best Health', (2006).

INVOLVE:
http://www.invo.org.uk
INVOLVE is funded by the National Institute for Health Research to promote and support active public involvement in NHS, public health and social care research. INVOLVE believe that involving members of the public leads to research that is more relevant to people's needs and concerns, more reliable and more likely to be used.

Association of Medical Research Charities:
http://www.amrc.org.uk
The Association of Medical Research Charities (AMRC) is a membership organisation of the leading medical and health research charities in the UK. AMRC aims to support the sector's effectiveness and advance medical research by developing best practice, providing information and guidance, improving public dialogue about research and science, and influencing government.

The James Lind Library:
http://www.jameslindlibrary.org
The James Lind Library is a web-based resource created to help people understand fair tests of treatments (clinical trials) in health care. It contains short essays explaining the principles of fair tests, and illustrates these with key passages and images from books and journal articles, commentaries, biographies, portraits, and other material showing how fair tests have developed over the centuries.

Further reading

Testing Treatments: Better research for better healthcare. Imogen Evans, Hazel Thornton, Iain Chalmers. British Library Publishing Division (2006)

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