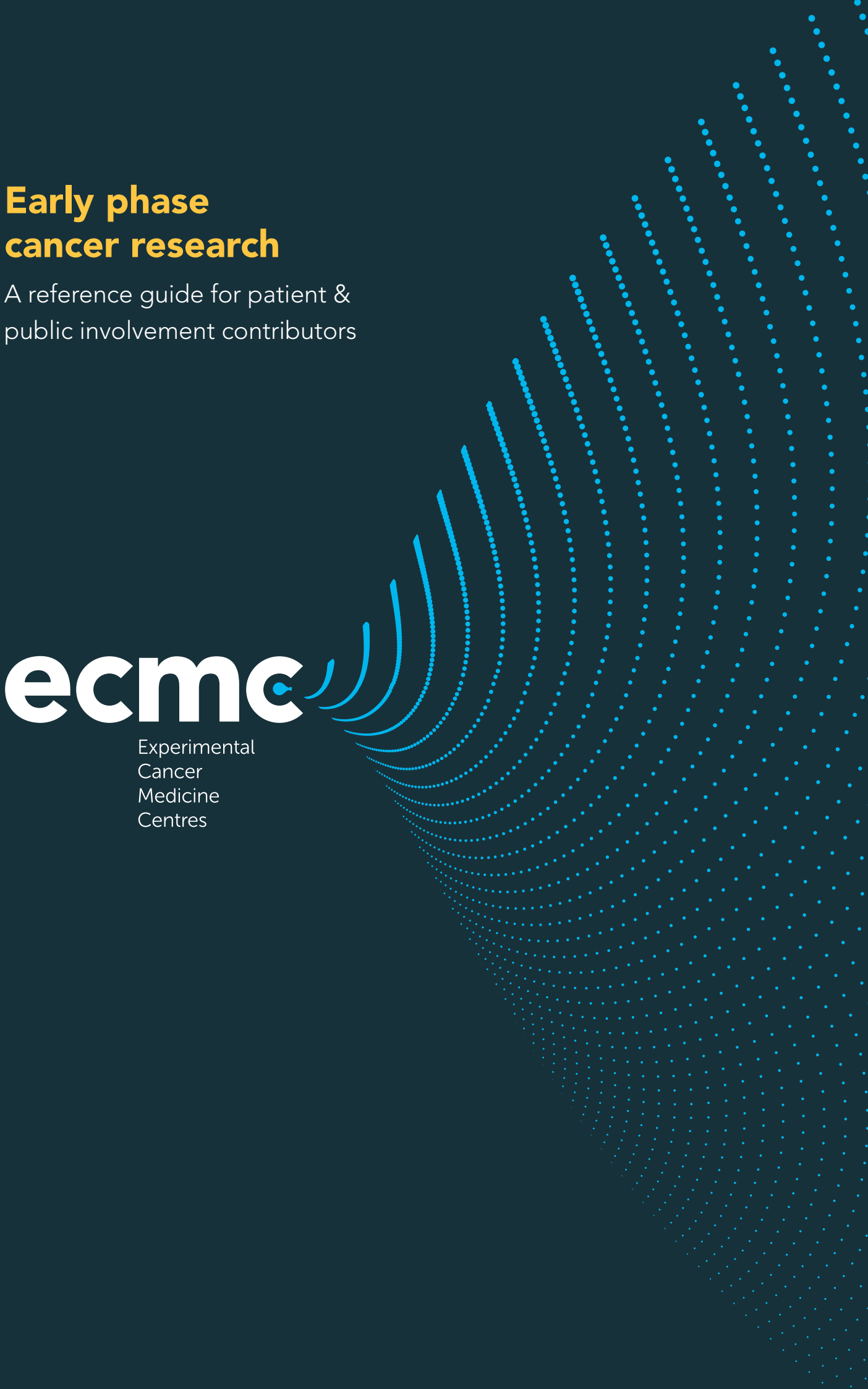
Early phase cancer research

A reference guide for patient & public involvement contributors



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Foreword

This booklet has been written by members of the ECMC network Patient and Public Involvement (PPI) Group. Each adult ECMC location is represented by 1 x member of staff (involved in PPI at their ECMC) and 1 x person affected by cancer [PaC] (involved in PPI at their ECMC).

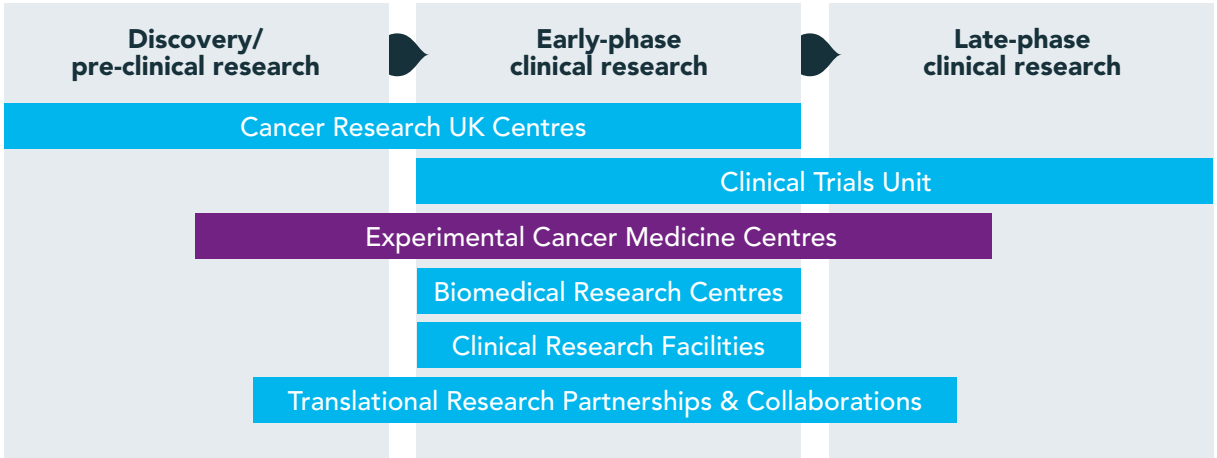
Introduction to the Experimental Cancer Medicine Centre (ECMC) network

The aim of the ECMC network is to speed up the development of new cancer medicines and other interventions to maximise patient benefit, through the support of local infrastructure. ECMCs are a partnership between the local university and NHS Trust/Health Board, and are expected to collaborate with the rest of the ECMC network to maximise the local resources and impact. ECMCs are jointly funded by Cancer Research UK and the National Institute for Health Research (NIHR) in England and the health departments for Scotland, Wales and Northern Ireland. Figure 1 shows how the ECMCs fit into the wider clinical research infrastructure landscape in the UK.

ECMCs help to fund the expertise and infrastructure (primarily staff) needed to conduct world-leading, early-phase cancer trials.

Further information on the ECMC can be found on our website: **www.ecmcnetwork.org.uk**

Figure 1: Clinical research infrastructure in the UK



This booklet will be reviewed annually to ensure that the information contained is still up to date. If you have any feedback on this booklet, please send it to **ecmcadmin@cancer.org.uk**

Purpose of guide

This reference guide has been written to support people affected by cancer who are taking part in PPI activities in early phase (Phase 1 and 2) cancer research. It gives a brief overview of the early phase cancer research world and highlights how this differs from later phase cancer research.

The information contained in this reference guide should help to give you an understanding of the terminology that you may encounter when taking part in any involvement activities to do with early phase cancer research and give you the confidence to raise questions during the course of your public involvement activity. This guide is intended to be used as both a reference document and a training aid, and it should be used to supplement existing training and education that PPI members receive.

At the beginning of each section, an overview has been given to highlight what will be covered and how it could be relevant to your experience.

Introduction to the research pathway

This section gives a brief overview of the research pathway; subsequent sections will go into more detail on the different stages. The research pathway explains the process from the first stages of testing a drug in a laboratory (pre-clinical research) through to the outcomes and feedback from patients receiving treatment.

At the beginning of the research pathway is pre-clinical research which is sometimes called basic science or laboratory-based research. This research develops scientific knowledge which is used as the building blocks for future patient treatment (along with diagnostics, procedures, devices etc).

A clinical trial or study is any medical research that involves people. Clinical trials are the only reliable way to test if a new treatment or procedure:

- Is safe
- Has side effects
- Works better than current treatments/procedures
- Helps patients feel better

Clinical trials provide the evidence that healthcare professionals, regulators and patients need to know in order to see which medicines or procedures work best in the treatment of cancer. This evidence is developed over different phases of clinical trials.

In order to ensure that trials are ethically and safely designed all trials are approved by Research Ethics Committees (REC) and the Health Research Authority (HRA) and Investigational Medicinal Product (IMP)/ device trials are approved by the Medicines and Healthcare products Regulatory Authority (MHRA).

Figure 2: Research Pathway and Clinical Trials of New Drugs

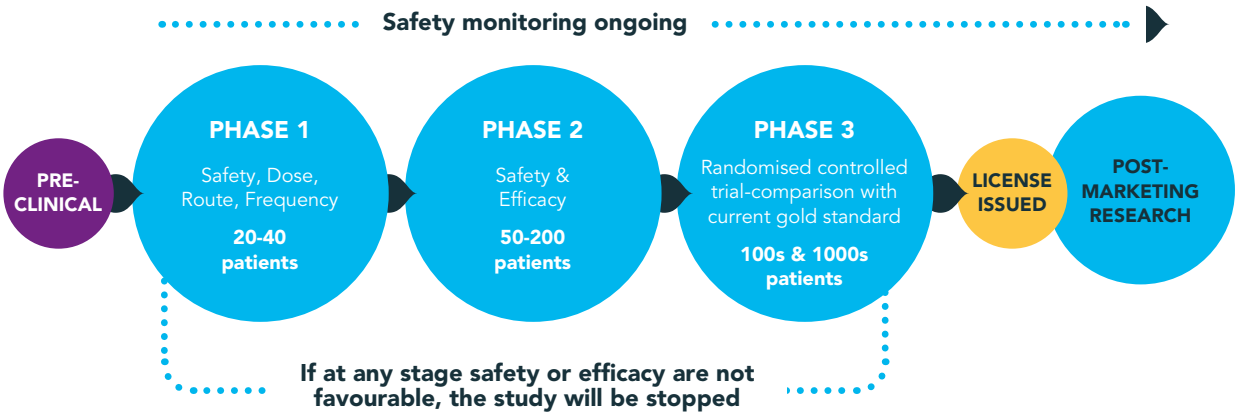


Figure 2 shows the research pathway and where Phase 1/2 trials fit with Phase 3 trials

Figure 3: Timeline for all phases of clinical trial development
Average drug development time is approximately 15 years with additional time for review

The average cost of developing a new agent is between £500 million and £1 billion. For every 1 drug to achieve regulatory approval, 10,000 compounds will be explored with 250 compounds going into preclinical testing (please see Figure 2 to see where in the research pathway this falls). Only 3-5% of compounds entering the preclinical phase will achieve regulatory approval.

Clinical trials are crucial in helping to develop new and better treatments for people with cancer. Early phase trials (Phase 1 and 2) carried out at ECMCs are important building blocks to developing treatments of the future.

Each clinical trial follows a set of rules, known as a protocol, to ensure it is well designed and as safe as possible, that it measures the right things in the right way, and that the results are meaningful.

Preclinical research and clinical research samples

This section gives information on the work that needs to be done in the laboratory before a drug is tested in humans, which is known as preclinical research. This section also covers some of the terminology that you may come across when reviewing any research done in the laboratory or if a clinical trial has any laboratory work as part of it.

Pre-clinical work

Before a drug makes it into the clinic and is tested in humans it will have undergone extensive pre-clinical work in the laboratory. This work helps to inform:

- Dose levels of the drug
- Potential side effects

The drug will have been tested in animals before going into a human in order to ensure that it is as safe as possible. Current UK law requires that all new drugs are tested on animals.

All the relevant pre-clinical information that has contributed to the design of the trial/study will be contained in the Investigational Brochure (IB) which all trial staff (and regulatory bodies) will have access to. The IB is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

Clinical Research

Drug development is the process of bringing a pharmaceutical drug to the market once a compound has been identified through the process of drug discovery. A Clinical Trial of an Investigational Medicinal Product (CTIMP) is a study that looks at the safety or efficacy of a medicine (or foodstuff or placebo) in humans as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004.

There is a very distinct pathway of drug development regarding cancer patients and their treatment, and this is reflective in the newest types of research or trial design. This is about personalising medicine to ensure the "right patient has the right treatment at the right time". This is described in more detail below. Please note that often the terms stratified, personalised and precision medicine are used interchangeably.

Personalised (or Precision) Medicine uses genetic and other information to diagnose and treat disease. Once research has been carried out with large groups of cancer patients it is hoped that it may be possible to predict response to treatments. The next step would then be to tailor cancer treatment very precisely to an individual person's cancer.

Stratified Medicine means looking at large groups of cancer patients to try and find ways of predicting which treatments cancers are more likely to respond to. It involves looking in detail at the cancer cells and their genetic make-up. Researchers want to find out if some treatments are more likely to work in cancers that have particular changes to their genes.

Biological samples

Many samples are taken for research purposes in early phase clinical trials. With the changing nature of trials and treatments, for example with the stratification of trials, more samples are needed. These include blood, urine, tumour and tissue samples. Blood samples are taken at frequent intervals in the first few cycles of a Phase 1 trial as the researchers need to measure how much of the drug is circulating (referred to as pharmacokinetics or PK) around the body at certain time points and how well it is being metabolised (broken down/used) in the body. Tissue samples are increasingly required to confirm eligibility for clinical trials as the move to more personalised treatments gather pace. In some trials, tissue and tumour samples are taken throughout the study to determine efficacy of the new agent and to find out how well it is working.

Below is some terminology and further information that relates to biological samples and may be included in study documentation for early phase cancer trials.

Pathology

Pathology is the science of the causes and effects of diseases, especially the branch of medicine that deals with the laboratory examination of samples of body tissue for diagnostic or forensic purposes.

There are a number of disciplines within pathology which include:

Histopathology: a discipline which examines a biopsy or surgical specimen by a pathologist after the specimen has been processed and stained sections of the specimen have been placed onto glass slides.

Molecular pathology: a discipline which is focused in the study and diagnosis of disease through the examination of specific molecules within organs, tissues or bodily fluids.

Biomarkers

A biomarker is a biological molecule found in blood, other body fluids, or tissues but may also be a simple physical measurement e.g. blood pressure. A biomarker has characteristics that are objectively measured and evaluated as an indicator of normal or abnormal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. A biomarker may be used to see how well the body responds to treatment for a disease or condition and can include molecular markers and signature molecules.

Pharmacokinetics (PK)

Branch of pharmacology dedicated to determining the fate of substances administered to a living organism. It attempts to analyse drug metabolism and to discover the fate of a drug from the moment that it is administered up to the point at which it is completely eliminated from the body. Pharmacokinetics is the study of how an organism affects a drug.

In relation to PK, ADME may be referenced, this stands for absorption, distribution, metabolism and excretion and describes the disposition of a pharmaceutical compound within an organism. This will be the reason why a patient may be requested to have a sample taken at 2am.

Pharmacodynamics (PD)

Branch of pharmacology concerned with the effects of drugs and the mechanism of their actions. PD places particular emphasis on dose-response relationships, that is, the relationships between drug concentration and effect. Pharmacodynamics is the study of how a drug affects an organism.

Both PK and PD influence dosing, benefit and adverse effects of drugs. See Appendix 1 for examples of PK/PD schedules.

Tumour Markers

Substances produced by a tumour or by the body as a response to cancer. Some tumour markers are only produced by one type of cancer, while others can be made by several cancer types. Tumour markers may be used to help diagnose cancer, or to see how patients are responding to treatment. Examples of tumour markers include CA125 blood test for ovarian cancer and Prostate Specific Antigen (PSA) blood test for prostate cancer.

Examples of samples include:

Circulating Tumour Cells (CTC): cancer cells that detach from a primary tumour and travel through the blood stream or lymphatic system to other parts of the body

Circulating tumour DNA (ctDNA): Tumour-derived fragmented DNA in the bloodstream that is not associated with cells. ctDNA should not be confused with circulating-free DNA (cfDNA)

Circulating free DNA (cfDNA): a broader term than ctDNA and describes DNA that is freely circulating in the bloodstream, but not necessarily of tumour origin.

Single Nucleotide Polymorphisms (SNPs): the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide.

Stem cells: undifferentiated biological cells that can differentiate into specialised cells and can divide to produce more stem cells.

Biobanking

Increasingly patients on clinical trials will be asked to provide a tumour sample as part of eligibility to enter a clinical trial. These will often be stored in what is known as a biobank. A biobank stores biological samples (usually human) for use in research. Since the late 1990s biobanks have become an important resource in medical research, supporting many types of contemporary research like genomics and personalised medicine. Increasingly tumours are being tested for genetic mutations following initial diagnosis. Many centres do this routinely for certain types of cancers i.e. those cancers known to have multiple mutations and for which we have targeted therapies.

See the Useful Links section for information on regulations which govern clinical trials, for example the Human Tissue Act which concerns activities relating to the removal, storage, use and disposal of human biological samples, including tissue outside of clinical trials.

Types of trials

This section gives information on the various phases of clinical trials – moving on from the laboratory setting into the clinical setting within the hospital.

Phase 1 trials
(sometimes written as Phase I)

Phase 1 trials are usually small trials, recruiting only a few patients, and their main aim is to determine the safety of a drug. They may be open to people with any type of cancer. Phase 1 trials can be described as Phase 1a or Phase 1b:

- Phase 1a are single ascending dose studies where the drug is observed to confirm its safety in patients.
- Phase 1b are multiple ascending dose studies where the pharmacokinetics (PK) (drug levels) and pharmacodynamics (PD) (effects on the body) of the drug are observed in patients in order to find out about its safety and tolerability.

When laboratory testing shows that a new treatment might help treat cancer, Phase 1 trials are done to find out:

- How much can safely be given and how often (what is the best dose of the treatment)
- What the side effects are
- How much is present in the blood, and for how long, after treatment
- Whether the treatment does what it was designed to (this may include shrinking down the cancer but that is not the main aim of these early trials).

The theories for how the drug will work in the clinic are all built on animal work in the laboratory.

Patients are recruited gradually onto Phase 1 trials. Although Phase 1 trials don't recruit many patients, they can take a long time to complete. The first few patients to take part (called a 'cohort' or group) are given a very small dose of the drug. This drug will have already been tested in animals at a higher dose.

If all goes well, the next group are given a slightly higher dose. The dose is gradually increased with each group. The researchers monitor the safety of the drug until they find the best dose to give. They will go up to the maximum tolerated dose (MTD), and then take a step-down approach. This is called a dose escalation study. The MTD is defined as the dose of drug that has an 'acceptable' level of toxicity or side effects. If you were to go over this dose you would be putting people at an 'unacceptable' risk for toxicity or side effects. Understanding MTDs is often a key objective of Phase 1 clinical trials.

Throughout this process patients will be closely monitored in order to manage the side-effects and toxicity. Some of these may be known from the pre-clinical work but there may also be new ones once the drug is tested in humans. Any adverse events that patients experience will be reviewed with them to see if they can be managed.

People taking part in Phase 1 trials often have advanced cancer and have usually had all the treatments available to them. The patients may be in a very different situation to those offered the chance to take part in a Phase 3/4 trial. They may benefit from the new treatment in the trial, but many won't. Phase 1 trials aim to establish doses and side effects, rather than treating a tumour. This work has to be done first, before the potential new treatment can be tested to see if it works. Patients will be asked to consent to each stage of the trial that they are involved in and are able to withdraw from the trial at any point.

Phase 2 trials
(sometimes written as Phase II)

Once the dose level has been found, a drug will move into a Phase 2 trial. Not all treatments tested in a Phase 1 trial make it to a Phase 2 trial. These trials may be for people who all have the same type of cancer or for people who have different types of cancer.

Phase 2 trials aim to find out:

- If the new treatment works well enough to test in a larger Phase 3 trial
- Which types of cancer the treatment works for
- More about side effects and how to manage them
- More about the best dose to use

Although these treatments have been tested in Phase 1 trials, there may still be side effects that the doctors don't know about. Drugs can affect people in different ways and the side effects experienced by all patients need to be recorded. Toxicities are assessed across patient groups using the Common Terminology Criteria for Adverse Events (CTCAE): **ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm** This ensures that all patients' side-effects are measured in the same way, that data captured is valid and patient safety is maintained.

Phase 2 trials are often larger than Phase 1. There may be up to 100 or so people taking part. Phase 2 trials can be single arm or randomised:

- Single arm trials are where all patients taking part in the trial receive the same treatment(s) at the same dose and regimen. These trials are often referred to as Phase 2a trials
- Randomised trials are where the new treatment is compared with another treatment already in use, with a dummy drug (placebo) or with the same treatment but at a different dose/regimen/combination; researchers put the people taking part into the treatment groups at random. These trials are often referred to as Phase 2b trials.

Phase 3 trials
(sometimes written as Phase III)

If the results of a Phase 2 trial show that a new treatment is safe and benefitting the patient group, it then moves into Phase 3 where it will be tested against existing treatments that are currently used in standard practice. Phase 3 trials involve hundreds to thousands of patients. If a treatment is successful in a Phase 3 trial, then it will be licenced. Generally, this means it becomes the standard treatment for patients with a particular type of cancer. The treatment may also move into further research (post-marketing research) to monitor the treatment.

As can be seen in the previous sections, there is a lengthy, complicated, and expensive process to follow when developing a compound pre-clinically, and through all phases of clinical trials. In order to progress beyond the earliest phases, details of the research, including results and problems encountered during the trial are shared between the different hospital sites which are open to recruitment.

With the increase in a more targeted approach to cancer research, and to avoid duplication of effort, scientists and doctors increasingly collaborate. This helps to reduce costs as well as the time it takes to develop new agents. Approximately 95% of all studies that start in Phase 1 do not achieve a licence, but the information gathered, even for those trials that fail to progress to the next level, will inform what happens next. Sharing ideas and experience through drug development, and the different phases of clinical trials will ensure better use of resources, and enable researchers to adapt studies in a timely, more efficient way.

Different types of early phase trials

Research is a dynamic environment where new ideas are being trialled all the time. This isn't an exhaustive list but covers the more common trial designs in use at the moment.

Adaptive Trial: evaluates a treatment by observing effects on patients (and possibly other measures such as side effects) on a prescribed schedule, and modifying parameters of the trial protocol in accordance with those observations. Modifications may include dosage, sample size, drug undergoing trial, patient selection criteria and 'cocktail' (drug) mix. Importantly the trial protocol is set before the trial begins and pre-specifies the adaption schedule and processes.

Basket Trial: where cancers of a different type are tested to see if they have particular molecular abnormality. If they do, patients with that abnormality are eligible to be treated with a new drug that targets that particular abnormality. This allows for new treatments to be tested across different cancer types. However many patients do need to be tested in order to find the handful that have the abnormality targeted by the new treatment.

Combination Trial: once it has been learnt how to use a new drug on its own, you might combine the new drug with standard treatment. Before that can be done routinely, it needs to be seen if the two treatments can safely be given together.

Drug Interaction Trial: once it has been learnt how to use a new drug on its own, you need to check that it is not affected by taking other medication. Likewise, a liver impairment or renal impairment trial is one in which patients with some loss of kidney function, respectively, receive a drug to confirm it will be safe to treat such patients in the future. Pharmacokinetics (PK) and Pharmacodynamics (PD) samples will be regularly taken in order to see the effect of the drug. This type of trial can also look at the effects of food intake on the pharmacokinetics of the drug. This is why patients will often be asked to not eat specific foods.

First in Man Trial: when a drug is being given to patients for the first time. The drug will, however, have been rigorously tested in the laboratory to show it works against cancer cells and looks to be safe. First in man can also be called first in human (FIH)

Umbrella Trial: where the impact of different drugs on different mutations in a single type of cancer are measured.

Window Trial: when a patient receives a new therapy for a period of time before starting standard treatment, including surgery/surgical options. The impact of the new therapy can therefore be evaluated without any disturbance from previous or simultaneous treatments.

Types of treatments

This section gives brief definitions to some of the different treatments for cancer that you may come across in your involvement work in early phase cancer research.

The different types of treatments for treating cancer are subject to new innovations coming aboard. The treatments listed below are some of the current treatments in use.

Advanced Therapy Investigational Medicinal Products (ATIMPs)

ATIMPs are medicinal products involving cells (cell therapy), genes (gene therapy) and tissues (tissue engineering). These innovative therapies combine aspects of medicine with cell biology, engineering and science in order to regenerate, repair or replace damaged tissues or cells and have huge potential for cancer treatments.

An ATIMP is a medicinal product which can be classed as either:

- **Gene Therapy (GTMP):** uses genes to treat or prevent disease, through regulation, repairing or replacing genetic sequence.
- **Somatic Cell Therapy (CTMP):** uses living cells from patients, which are manipulated through laboratory processes, in order to treat or prevent a disease through pharmacological, immunological or metabolic action of its cells or tissues.
- **Tissue Engineered Products (TEPs):** is a product which contains engineered (altered) cells or tissues or is used in, or administered to, patients with a view to regenerating, replacing or repairing human tissue.
- **Combined Advanced Therapy Products:** tissue or cell therapy (as above) associated with a medical device.

These types of advanced therapies are subject to complex clinical trial protocols and are highly regulated in order to ensure safety and efficacy.

Biological Therapies

- **Immunotherapy:** uses our own immune system to fight cancer. It is a type of biological therapy that uses substances to stimulate or suppress the immune system to help fight cancer, infection and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way.
- **Targeted Therapies:** targeted cancer drugs work by 'targeting' those differences that help a cancer cell to survive and grow. Targeted therapies are a biological treatment (often called biologic) that use drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells.

  Some targeted therapies block the action of certain enzymes, proteins or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapy may have fewer side effects than other types of cancer treatment. Most targeted therapies are either small molecule drugs or monoclonal antibodies (an antibody that is made so it binds to only one substance). Monoclonal antibodies have MAB at the end of their name e.g. Trastuzumab.
- **Vaccines:** a type of biological therapy that uses a substance or a group of substances to stimulate the immune system to destroy the tumour or infectious microorganisms such as bacteria or viruses.

Other Treatments

Chemoprevention: the use of drugs or vitamins to try to reduce the risk of or delay the development or recurrence of cancer.

Chemoradiotherapy: treatment that combines chemotherapy with radiotherapy. Also called chemoradiation.

Chemotherapy: an anti-cancer drug treatment. It is a treatment that uses cell killing drugs (cytotoxic agents) to kill cancer cells. This type of treatment is not targeted and causes damage to all cells, particularly those that divide rapidly i.e. hair, gut lining, blood cells etc.

Device (medical device): an instrument, tool, machine, test kit or implant that is used to prevent, diagnose or treat disease or other conditions. Medical devices range from tongue depressors to heart pacemakers and medical imaging equipment.

- **Imaging:** in medicine, a process that makes detailed pictures of areas inside the body. Imaging uses methods such as x-rays (high-energy radiation), ultrasound (high-energy sound waves), radio waves and radioactive substances.

  In treating cancer, imaging is used to help diagnose disease, plan treatment, or find out how well treatment is working. Examples of imaging procedures are computed tomography (CT), positron emission tomography (PET), ultrasonography, magnetic resonance imaging (MRI) and nuclear medicine tests.

Hormone therapies: medicines that block the effect of hormones in the body. These therapies block or lower the amount of hormones in the body to stop or slow the growth of cancer. Used to treat cancers that use hormones to grow (e.g. breast, prostate, ovarian, endometrial and kidney cancers).

Radiotherapy: the use of radiation from x-rays, gamma rays, neutrons, protons and other sources to kill cancer cells and shrink tumours. Radiation may come from a machine outside the body (external-radiation therapy), or it may come from radioactive material placed in the body or near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabelled drug, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Stem cell or bone marrow transplant: high doses of chemotherapy (with or without radiotherapy) are given and then stem cells or bone marrow are transplanted, either from the patient's own cells (autologous transplant), or from a donor (allogeneic transplant). Stem cell or bone marrow transplants are used to treat a variety of conditions such as blood cancers (leukaemia, lymphoma and myeloma) but these can also be undertaken in other indications i.e. severe aplastic anaemia (bone marrow failure), Sarcoma, Multiple Sclerosis etc.

Surgery: a procedure (operation) to remove cancerous tissues from the body. Surgery can be done to help diagnose cancer (biopsy) or to treat cancer.

Working with funders

Early phase cancer research is funded by different stakeholders who often need to work together in order to both fund and deliver the research. When you are involved in activities to do with early phase cancer research you may come across trials or research funded by those from the following sectors:

Commercial funders

Commercial partners can fund a study through a financial contribution or contribution in kind with drugs/assays etc. The pharmaceutical industry develops, produces and markets drugs or pharmaceuticals for use as medicines. Pharmaceutical companies may deal in generic or brand medicine and medical devices.

The benefits of working with pharmaceutical companies is that we get to improve patient outcomes through working together to ensure that patients get optimal care, including appropriate use of cost-effective innovative medicines with support to help them maximise the benefits of treatment. Industry partnerships are vital in driving the development of the cancer drugs for tomorrow and the UK has an incredibly strong science foundation from which to adapt to the latest scientific breakthroughs. Developing a new drug can take around 15 years and cost between £500million and £1billion.

Government

The devolved governments in the UK support the delivery of early phase cancer research via their health departments. They support research by both funding specific trials/research and providing funding for the buildings and people who support the running of these trials.

Charity

Specific disease-related charities provide funding for research through a variety of mechanisms, from infrastructure to grants for investigator-led programmes, projects and training fellowships. Charity funding spans the research pipeline, and their portfolio includes research into a wide variety of types of cancer. See the link below for full details of charities funding cancer research.

www.amrc.org.uk

Patient experience on early phase cancer trials

The purpose of this section is to provide some examples of why patients agree to take part in early phase cancer trials and what their experience is of going on such trials. A patient who is offered the opportunity to take part in an early phase trial often has cancer which cannot be treated or is likely to return.

Alan's story

Alan was originally diagnosed with malignant melanoma in 2011 and had an excision biopsy followed by wider local excision with split skin graft. Two years later metastatic melanoma was diagnosed, and Alan underwent further surgery to remove disease in his right femur, with further surgery undertaken several months later as the disease spread more widely. His tumour tissue was analysed for mutations at this point, to establish what treatment would be best to tackle his disease.

Following a PET CT scan the following year confirming widespread disease, Alan commenced first line systemic treatment with immunotherapy but, due to side effects, had to stop treatment after only three cycles. Despite this, Alan had a partial response to treatment, and once he had recovered from the side effects, he commenced another type of immunotherapy which he tolerated well.

Alan had a good clinical response to this second line of treatment which continued for over a year, but unfortunately his disease progressed again, and he underwent further surgery.

At the beginning of 2017 Alan was referred to the Early Phase Clinical Trials unit and consented to take part in a clinical trial. This involved regular visits to the unit to receive novel therapy. He tolerated treatment well and had an excellent response but at the end of 2018 his disease recurred, albeit locally. He is currently awaiting surgery to have this local disease removed. Alan was asked how he felt about taking part in a clinical trial.

In Alan's own words...

What it feels like to be chosen for a trial

To be chosen for a trial initially triggers many emotions:

- **Hope** – that there is a plan and something to aim for.
- **Fear** – of the unknown. How will the drug affect you short term / long term? Will it work for you and for how long?
- **Satisfaction** – in the knowledge that although the trial may not benefit you in the long term, it may help others as the drug develops, and hopefully becomes more effective.

What it feels like to be on a trial

- A rollercoaster of a ride. In the early days, although I was made aware of the many possible side effects, the reality can be a little daunting as some of the effects take hold. The first few weeks can feel like 'why am I putting myself through this?'
- However, as the weeks go by the side effects settle down, some disappearing altogether. In my case the side effect that stayed with me was skin rashes which were treatable and tolerable.
- As treatment went on and I met different patients, I was reminded of an old saying of mine – 'there is always someone worse off than you.'
- You realise the dedication of all the staff, nurses, doctors and consultants alike.
- The 'forgotten' people when you are going through this are your family and friends. It is hard for them to understand the process, and it is good to help them by continuous communication from yourself.
- The things that stay with you throughout: Hope, fear and satisfaction, and above all, uncertainty.
- But grateful that so many people care.

National Cancer Patient Experience Survey

This survey has been designed to monitor national progress on cancer care; to provide information to drive local quality improvements; to assist commissioners and providers of cancer care; and to inform the work of the various charities and stakeholder groups supporting cancer patients. There is a question about if a patient has been given the opportunity to take part in cancer research:

www.ncpes.co.uk/index.php/reports

Glossary

The following terms and acronyms are not all referenced in the booklet however you may come across them in your involvement work.

ABPI	The Association of the British Pharmaceutical Industry: A trade association for UK pharmaceutical companies.
AE	Adverse Event: any unexpected occurrence in a patient administered a drug which doesn't necessarily have a causal relationship with this treatment.
Allogeneic stem cell transplant	Stem cells donated to the patient from another person who is a genetically matched stem cell donor. There are a number of different types of allogeneic transplants including Sibling transplants, Matched unrelated donor (MUD) transplants, Cord blood transplants or Haploidentical transplants.
Analyte	Analyte could be a drug, a biochemical substance or a cell in an organism or organic sample.
AR	Adverse Reaction: an unexpected or dangerous reaction to a drug.
Assay	A procedure in molecular biology measuring the presence, amount or activity of the analyte.
ATIMP	Advanced Therapy Investigational Medicinal Products are medicinal products involving cell or gene therapy or tissue engineering.
Autologous stem cell transplant	This type of transplant the patient is their own stem cell donor. These cells are collected in advance (while the patient is in remission) and returned to the patient at a later stage.
Biopsy	A surgical specimen.
BRC	Biomedical Research Centre: topic-focused centre with facilities and research active clinicians/academics/research nurses to run clinical projects.
cfDNA	Circulating free DNA (cfDNA) are degraded DNA fragments released to the blood plasma.
Challenge Agent	Challenge agents are usually given to trial subjects to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
CI	Chief Investigator: the lead investigator with overall responsibility for the research. In a multi-site study, the CI has coordinating responsibility for research at all sites. The CI may also be the PI at the site which they work. In the case of a single-site study, the CI and PI will normally be the same person and are referred to as PI.
Compound	A compound is a chemical substance that combines two or more elements.

Cord blood transplant	If a sibling or unrelated donor is not available, a patient may be offered a cord blood transplant instead. Cord blood stem cells don't need to be well matched compared to other sources of stem cells as they are not as mature as blood stem cells. This means it can be easier to find a suitable cord match.
CRF (i)	Clinical Research Facility: hospital-like facility with consulting rooms, standard patient beds, ward medical equipment, research nurses supporting only research.
CRF (ii)	A Case Report Form is a data collection tool provided by a sponsor on which the clinical trial data is recorded for each participant, such as weight, lab results, symptoms.
CRN	Clinical Research Network
CRO	Clinical Research Organisation or Contract Research Organisation: A person or an organisation (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.
CT	Computed Tomography (imaging procedure).
CTC	Circulating Tumour Cells: these are cancer cells from the primary tumour that escaped into the bloodstream to circulate around the body.
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product is a study that looks at the safety or efficacy of a medicine/foodstuff/placebo in humans, as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004.
CTMP	Somatic Cell Therapy: medicinal product using living cells from patients.
CTU	Clinical Trials Unit: design and manage CTIMPs, sometimes in specialist clinical areas, such as cancer, or types of trials, such as RCTs.
DH	Department of Health (for England)
ECMC	Experimental Cancer Medicine Centre
Efficacy	The ability to produce a desired or intended result.
Enzyme	Any of a group of chemical substances that are produced by living cells and cause particular chemical reactions to happen while not being changed themselves.
Excision biopsy	A biopsy in which an entire lesion is removed.
Feasibility	The process of reviewing the protocol to determine whether or not a study can be safely and effectively delivered.
GCP	Good Clinical Practice: GCP is an international ethical and scientific quality standard for designing, recording and reporting studies. The aim of GCP is to ensure the rights, safety and wellbeing of study participants are protected and research data is high quality.
Genomics	Study of genes and their functions and related techniques.
GLP	Good Laboratory Practice: standard for laboratories involved in pre-clinical analyses (e.g. animal, in vitro); does not apply to laboratories analysing samples from clinical trials involving humans.
GMP	Good Manufacturing Practice: quality assurance standard for producing IMP, medicinal products.

GTMP	Gene Therapy: a medicinal product using genes to treat or prevent a disease.
Haploidentical transplant	A haploidentical transplant uses healthy, blood forming cells from a half matched donor to replace the unhealthy ones; haploidentical donors are typically family members (i.e. mother, father, half siblings).
HFEA	Human Fertilisation and Embryological Authority
HRA	Health Research Authority
HTA	Human Tissue Act or Human Tissue Authority
IB	Investigator's Brochure: A compilation of clinical and pre-clinical pharmacological/biological data relevant to the use of that IMP(s) in human subjects (one single IB for all trials using the same IMP).
Immunological	A science that deals with the immune system and the cell-mediated and humoral aspects of immunity and immune responses.
IMP	Investigational Medicinal Product: an unlicensed new drug, an existing drug tested outside its licence or existing drugs tested against each other for their efficacy/safety. The MHRA provides advice to help researchers decide if their product is an IMP.
ICF	Informed Consent Form: Informed consent is an ongoing process that must occur before any clinical trial related procedures are conducted. The process consists of a document (ICF) and a series of conversations between the clinical trial participant and the principal investigator (PI) and delegated health care professional, as appropriate. In the ICF and conversations, patients are given important information, including possible risks and benefits, about a medical procedure or treatment, genetic testing, or a clinical trial. This is to help them decide if they want to be treated, tested or take part in the trial.
LCRN	Local Clinical Research Network
Liquid biopsy	A test done on a sample of blood to look for cancer cells from a tumour that are circulating in the blood or for pieces of DNA from tumour cells that are in the blood.
MDT	A multidisciplinary team is a group of health care workers who are members of different disciplines (professions e.g. psychiatrist, social workers etc), each providing specific services to the patient.
Metabolic action	Relating to metabolism, the whole range of biochemical processes that occur within us (or any living organism). Metabolism consists of anabolism (the build-up of substances) and catabolism (the breakdown of substances).
MHRA	Medicines and Healthcare products Regulatory Agency: The UK Competent Authority (CA) and licensing authority for medicines and medical devices.
Molecule	A molecule is the smallest particle in a chemical element or compound that has the chemical properties of that element or compound.
Monitor	The person designated by the sponsor to perform site visits and conduct the monitoring process; e.g. check whether there are any deviations from the protocol and that all source data was transferred into the Case Report Forms correctly.

MRI	Magnetic Resonance Imaging (imaging procedure).
MTD	Maximum Tolerated Dose
MUD transplant	Matched unrelated donor transplants: if a patient doesn't have the options of a sibling match they may be offered a MUD transplant. This is when the new stem cells come from a stranger whose tissue type matches that of the patient.
Multiple ascending	A Multiple Ascending Dose study is one of the earliest studies performed in the clinical development of a drug, preceded only by an initial Single Ascending Dose study. "Multiple" indicates that each subject receives multiple doses of the study drug.
Mutation	A change in genetic/DNA sequence that makes a gene, so that the sequence differs from what is found in most people.
NHS	National Health Service
NICE	National Institute for health and Clinical Excellence: develop evidence-based guidelines on the most effective ways to diagnose, treat and prevent disease and ill health.
NIHR	National Institute for Health Research: established by the Department of Health for England in 2006 to provide the framework through which DH will position, manage and maintain the research, research staff and infrastructure of the NHS in England as a virtual national research facility.
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP (or non-IMP)	Non-Investigational Medicinal Product: product used alongside IMP but not directly under investigation in the research study, e.g. challenge agent.
NOCRI	National Office for Clinical Research Infrastructure
PaC	Person/People affected by cancer: this includes people who have or have had cancer themselves; loved ones (family and friends) of people who have or have had cancer; and people who have cared for people with cancer (not in a professional context).
Participant outcomes	Definition of a health outcome. "A planned measurement described in the study protocol that is used to determine a change in health status as a result of interventions on participants in a clinical trial."
Personalised Medicine	Personalised (or Precision) Medicine uses genetic and other information to diagnose and treat disease. Once research has been carried out with large groups of cancer patients it is hoped that it may be possible to predict response to treatments.
PET	Positron Emission Tomography (imaging procedure)
PD	Pharmacodynamics: is the study of how a drug affects an organism.
Pharmaceutical	Relating to medicinal drugs, or their preparation, use, or sale. For example: 'a pharmaceutical drug' 'the pharmaceutical industry'
Pharmacological	The study of medicines and drugs, including their action, their use, and their effects on the body.
PI	Principal Investigator: The lead person at a single site designated as taking responsibility within the research team for the conduct of the study.

PIS	Participant or Patient Information Sheet: An information leaflet given to those who have been invited to participate in a research study. The sheet is designed to provide the potential participant with sufficient information to allow that person to make an informed decision on whether or not they want to take part.
PK	Pharmacokinetic: is the study of how an organism affects a drug.
PPIE (or PPI)	Patient and Public Involvement and Engagement
Pre-screeing	The process of identifying eligible patients prior to approaching them to determine if they are willing to consent to participate in the study.
Protein	A nutrient found in food (as meat, milk, eggs and beans) that is made up of many amino acids joined together, is a necessary part of the diet, and is essential for normal cell structure and function.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.
QA	Quality Assurance: A process that looks at activities or products on a regular basis to make sure they are being done at the required level of excellence.
QC	Quality Control in clinical trials means the procedures which insure protection of human subjects from research risk, reliability of data, and thereby assures internal consistency.
QLQ (or QoL)	Quality of Life Questionnaire
Radiolabelled	To tag (a hormone, enzyme, or other substance) with radioactive tracer.
RCT	Randomised Controlled Trial: a clinical study in which two (or more) forms of care are compared; the participants are allocated to one of the forms of care in the study, in an unbiased way.
REC	Research Ethics Committee: authorised by HRA to review study documents for research taking place in the NHS, or social services. Some REC specialise in clinical trials, or topics such as research in children. All research in NHS/social services must have been reviewed by a UK REC.
Regimen	A prescribed course of medical treatment, diet or exercise for the promotion or restoration of health.
SAE	Serious Adverse Event: an adverse event which results in either: death; is life threatening; requires hospitalisation; results in persistent or significant disability/ incapacity or congenital anomaly/birth defect.
SAR	Serious Adverse Reaction: an adverse reaction which results in either: death; is life threatening; requires hospitalisation; results in persistent or significant disability/ incapacity or congenital anomaly/birth defect.
Screening	Screening occurs after the ICF is signed and involves a series of assessments, or measurements, to confirm the participant is eligible and safe to participate in the trial. These may be conducted over a number of days or weeks dependant on the protocol requirements.
Sibling or matched related donor (MRD) transplants	If a patient has any brothers or sisters, the hospital will often ask to test them before anyone else. This is because siblings (with the same mother and father) have a much higher chance of having a matching tissue type.

Single ascending	A single-ascending dose study is the earliest study performed in the clinical development of a drug (see also multiple ascending).
SIV	Site Initiation Visit is a monitoring visit that take place after the Site Selection Visit. It is a visit that happens after the sponsor has already selected the site for participating in a clinical trial.
SNPs	Single Nucleotide Polymorphisms are the most common type of genetic variation among people.
SOP	Standard Operating Procedure: detailed written instructions designed to achieve uniformity of the performance of a specific function.
Split skin graft	An operation to mend a wound with a patch of skin from another part of the body.
Sponsor	In relation to a clinical trial, the sponsor is an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.
Stratified Medicine	Stratified medicine means looking at large groups of cancer patients to try and find ways of predicting which treatments cancers are more likely to repond to. It involves looking in detail at the cancer cells and their genetic make-up. Researchers want to find out if some treatments are more likely to work in cancers that have particular changes to their genes.
SUSAR	Suspected Unexpected Serious Adverse Reaction: a Serious Adverse Reaction (SAR) which is unexpected (i.e. its nature and severity is not consistent with the known information about that product from the Investigator's Brochure (IB)) and suspected, as it is not possible to be certain of causal relationship with the IMP.
Systemic	Affecting the entire body, rather than a single organ or body part.
TEP	Tissue Engineered Products are products that contain or consist of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
TMF	Trial Master File: file with essential documents held by the Chief Investigator/ Sponsor organisation.
Toxicities	The extent to which something is poisonous or harmful.
WLE	Wide local excision: A surgical procedure to remove a small area of diseased or problematic tissue with a margin of normal tissue. The results of a WLE will determine any future treatments if needed.

Useful links

Education

Free patient resources, including 'Understanding Clinical Trials for Cancer' leaflet
Clear information on what a trial is, the different types of trials and how they work.
publications.cancerresearchuk.org/publication/understanding-clinical-trials-cancer

Free online course for specialist nurses: Demystifying Targeted Cancer Treatments
Learn from experts and gain a deeper understanding of how targeted treatments work to support your patients.
www.futurelearn.com/courses/targeted-cancer-treatments

Free online course: Improving healthcare through clinical research
Learn about how medical treatments are discovered, tested and evaluated to improve healthcare for your patients.
www.futurelearn.com/courses/clinical-research

FutureLearn course
FutureLearn provides many online courses and is often updating their course content. Visit their website to see what they currently have on offer.
www.futurelearn.com

Clinical Trials

Cancer Research UK clinical trials database
Reliable, easy-to-understand information on cancer clinical trials for you and your patients.
www.cruk.org/trials

National Institute for Health Research (NIHR)'s Be Part of Research
Guidance on how trials work and help to connect your patients to researchers running trials they might be interested in.
bepartofresearch.nihr.ac.uk

Patient and Public Involvement

INVOLVE
Part of and funded by the NIHR to support active public involvement in NHS, public health and social care research.
www.invo.org.uk

James Lind Alliance
Brings patients, carers and clinicians together in Priority Setting Partnerships (PSPs) to identify and prioritise the Top 10 uncertainties, or unanswered questions, about the effects of treatments.
www.jla.nihr.ac.uk

PPI in the NIHR
www.nihr.ac.uk/patients-carers-and-the-public

PPI at Cancer Research UK
www.cancerresearchuk.org/support-us/volunteer/patient-involvement-at-cancer-research-uk

PPI in the Chief Scientist Office, Scotland
www.cso.scot.nhs.uk/patientspublic

PPI in Health and Care Research Wales
www.healthandcareresearch.gov.wales/get-involved-in-research

PPI in the Public Health Agency, R&D Division (Northern Ireland)
www.research.hscni.net/personal-and-public-involvement-ppi-research

PPI in the National Cancer Research Institute (NCRI)
www.ncri.org.uk/patient-and-public-involvement

Clinical and Translational Radiotherapy (CTRad) Research Working Group
Details on PPI in the work of CTRad and their input in designing trials.
ctrad.ncri.org.uk/research-support/patient-and-public-involvement

Regulations

Clinical Trial Regulations
The Human Tissue Act: activities relating to the removal, storage, use and disposal of human biological samples, including tissue outside of clinical trials are regulated by the Human Tissue Act (2004). Consent is the fundamental principle of the legislation and underpins all activities. This act covers England, Wales and Northern Ireland. There is separate legislation in Scotland, the Human Tissue (Scotland) Act 2006 and the Human Tissue Authority performs certain tasks on behalf of the Scottish government (approval of living donation and licencing of establishments storing tissue for human application). Further information can be found on the Human Tissue Authority website: **www.hta.gov.uk**

Health Research Authority (HRA)
Protects and promotes the interests of patients and the public in health and social care research.
www.hra.nhs.uk

Medicines and Healthcare products Regulatory Agency (MHRA)
Regulates medicines, medical devices and blood components for transfusion in the UK
www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

Acknowledgements

The following sources were used to help to provide the content for the Types of trials and Types of treatments sections of the booklet:

ECMC website – **www.ecmcnetwork.org.uk/what-are-clinical-trials**

CRUK website – **www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are**

CRUK website – **www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment**

Leeds CRUK Centre produced booklet 'Phase 1 or early phase clinical trials – information for patients'

Appendices

Appendix 1: Example PK/PD schedules

Example 1

An example of a PK/PD schedule for a FIH Phase 1 trial is given below, each blood sample type will be taken in a different tube. You may see this type of information if you are asked to review a trial protocol or patient information sheet.

	Screening	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	28 days after completion	70 days after completion
PD Samples									
Archival tumour tissue to measure biomarker expression	X								
Tumour biopsy to measure biomarker expression and drug levels in tumour			X ***						
Blood test to measure specificity of infusion reactions		2x1mL*	1x1mL	1x1mL	1x1mL	1x1mL	1x1mL		
Blood test to measure immune response to drug		1x4mL		1x4mL			1x4mL	1x4mL	
Blood test to measure drug binding		2x5mL*		1x5mL					
Blood test to measure circulating biomarkers		1x3mL			1x3mL			1x3mL	
Blood test to measure antibodies		1x3mL		1x3mL				1x3mL	
Blood test to measure changes in cytokines		6x2mL**	1x2mL						
Blood test to measure serum biomarkers	1x5mL								
Blood test to measure immune cells		1x5mL		1x5mL			1x5mL		
PK Samples									
Blood test to measure PK		6x5mL**	1x5mL					1x5mL	1x5mL

mL millilitre; 1 teaspoon = approximately 5mL

* Pre-dose and post dose

** Pre-dose and 2hr, 4hr, 6hr, 24hr, 48hr post-dose

*** Optional

Example 2

Trial A

Clinical Study Protocol xxxxx Amendment 3, EudraCT: xxxxxxxxx

Table 1-2 Pharmacokinetic Sampling Schedule for ARM 1 (xxxx + yyyy)—Escalation Phase

Sampling Time (Cycle 1, Day 10) xxxx / yyyy
Predose X X
0.5 hour postdose (± 5 minutes) X X
1 hour postdose (± 5 minutes) X X
2 hours postdose (± 15 minutes) X X
4 hours postdose (± 15 minutes) X X
6 hours postdose (± 30 minutes) X X
8 hours postdose (± 45 minutes) X X
24 hours postdose (± 1 hour) (Day 11) Xa Xa
48 hours postdose (± 2 hours)b (Day 12) X

See Section a.b.c and the Laboratory Manual for specific instructions pertaining to pharmacokinetic (PK) sampling and processing.

PK samples may be drawn at the time of AEs leading to treatment interruption/reduction.

a The 24-hour postdose PK sample is collected before xxxx and yyyy dosing on Cycle 1, Day 11.

b The 48-hour postdose PK sample is collected before xxxx dosing on Cycle 1, Day 12

Appendix 2: Flow Sheet

Example of a flow sheet, taken from a Patient Information Sheet (PIS) which illustrates how involved taking part in a clinical trial can be.

Tests & procedures	Treatment period (1 year)				Follow-up	Additional follow-up (every 3 months)
	Day 1, (1st day of dosing)	**Weeks 1-13**	**Weeks 15-29**	**Weeks 31-49**	**Visit 1 & 2 (at hospital)**	**At hospital / on phone**
Physical Exam: Weight; Vital Signs & performance status (see how well you are)	●	●	●	●	●	
Review of your medication & any side effects you might be having	●	●			●	● (just side effects)
Pregnancy Test (blood/urine) for women able to become pregnant	● (within 72 hrs of dosing)	● Every 4 wks				●
Safety Bloods Routine blood test for safety purposes (about 2 ½ teaspoons (tsp)) – **can be done up to 72 hrs prior to dosing**	●	● Every 4 wks			● (only at visit 2 if still having side effects)	
Research Bloods – about 2 tsp/8.5mls to about 4 tsp/20 mls To measure how the drug(s) is broken down & the amount circulating in your bloodstream. All samples are collected before your dosing	●	● wks 5 & 9	● wks 15 & 21	● wk 37	●	
Research Bloods – about 2 tsp to about 4 tsp To see if your body's own immune system produces proteins that recognise the study drug(s). All samples are collected before your dose.	●	● wks 5 & 9	● wks 15 & 21	● wk 37	●	
Research Bloods – from 2 tsp to up to 17 ½ tsp / 86.5 mls To test for certain markers in your blood (substances such as cells, proteins, DNA, RNA or other members)	● 17 ½ tsp	● ~ 12 ½ tsp @ wk 7 & 17 ½ tsp @ wk 13	● ~ 17 ½ tsp @ wk 29	● ~ 2 tsp of blood @ wk 45		
Optional stool (faeces) sample for bacterial testing (called a microbiome test). More information on what's involved is covered in appendix A.	● wk 1	● wk7	● wk 29			
Complete Health Questionnaires (prior to dosing) – 3 in total	●	● wk 5 & 9	● wk 13, 17, 21, 25	● wk 33, 37, 41 & 49	● (3 questionnaires)	● (3 questionnaire)
Study Drug(s) infusion (as described in section 6)	**Infusion** @ wk 1, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49					
Optional biopsy of affected organs if your cancer returns.	●					
Tumour Assessment (by CT or MRI) (chest, neck, abdomen, pelvis, any other known sites of disease)	Every 12 wks for the first 36 months and then every 6 months until your disease has worsened					
PET CT may be required (4 PET CT maximum – 2 at screening and 2 at progression) Your doctor can tell you more about what a PET scan involves	●					

Notes

You may wish to make some notes in this section if you have any queries about anything that you have read. You can then follow-up on this in discussion with your PPI contact or local PPI group.

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