Successful nursing
in a Phase I environment

ecmc

Experimental
Cancer
Medicine
Centres

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Introduction

Purpose of this booklet

This booklet has been written by members of the ECMC Research Nurse Network Group Steering Committee who are sharing their experiences on how they deliver Phase I cancer trials. This booklet demonstrates how early phase cancer trials differ (or don't) from later phase trials. The purpose of this booklet is to support the training day (Successful nursing in a Phase I environment) and it does not contain all the information you will need to know. By attending the training day, you will be able to hear from other nurses working in this area (both experienced and new), find out about how research trials are run at their sites, and the issues and challenges they face and have overcome.

Please note that sites work in different ways, therefore this booklet contains generalisations and you are encouraged to find out about the practices and Standard Operating Procedures (SOP) at your own site.

Introduction to the ECMC network and Research Nurse Network Group

The Experimental Cancer Medicine Centres (ECMC) network is an initiative funded in partnership by Cancer Research UK and the four health departments of England, Scotland, Northern Ireland and Wales. Launched in 2007 with a total investment by the funders of over £100 million, this infrastructure award supports a network of 18 adult centres (of excellence) and 11 paediatric locations throughout the UK. By bringing together world-class scientific and clinical expertise the ECMC network advances the boundaries of cancer care.

ECMC Research Nurse Network Group: the nurses promote quality care for patients taking part in early phase cancer research through peer support, training and guidance for those involved in early phase and translational research.

Remit of ECMC Research Nurse Network Group:

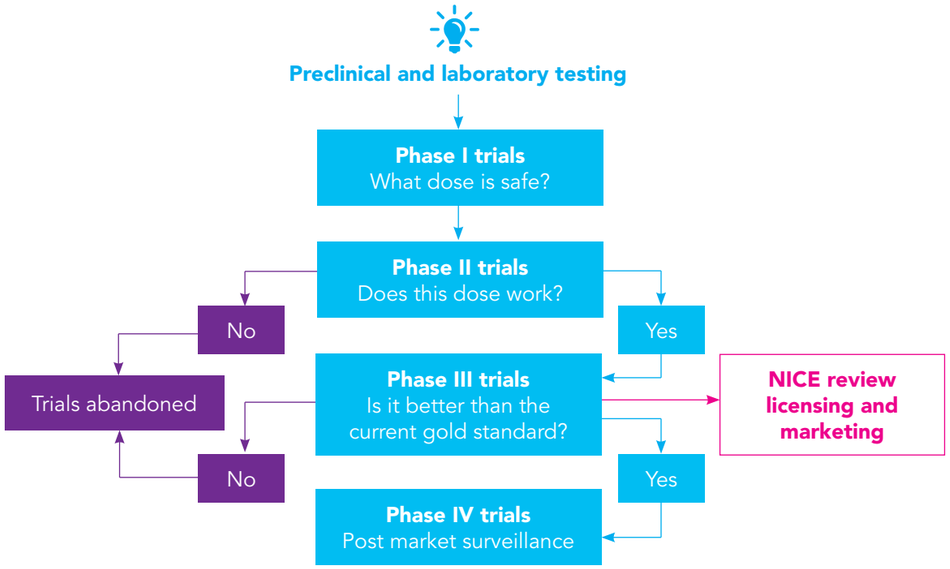
- Contribute to achieving the aims of the ECMC initiative
- Identify priorities for the development of the group and take them forward
- Facilitate the sharing of expertise and experience across the ECMC network and promote collaboration amongst research nurses working in the experimental cancer medicine arena
- Produce guidelines and recommendations where required
- Work with the ECMC Programme Office to communicate the activities of the group
- Collaborate with other research organisations in order to maximise the group's impact
- Raise the profile of early phase research nurses and the ECMC network.

Further information on the group, including the current steering committee members can be found on the ECMC website: **www.ecmcnetwork.org.uk/nurses**

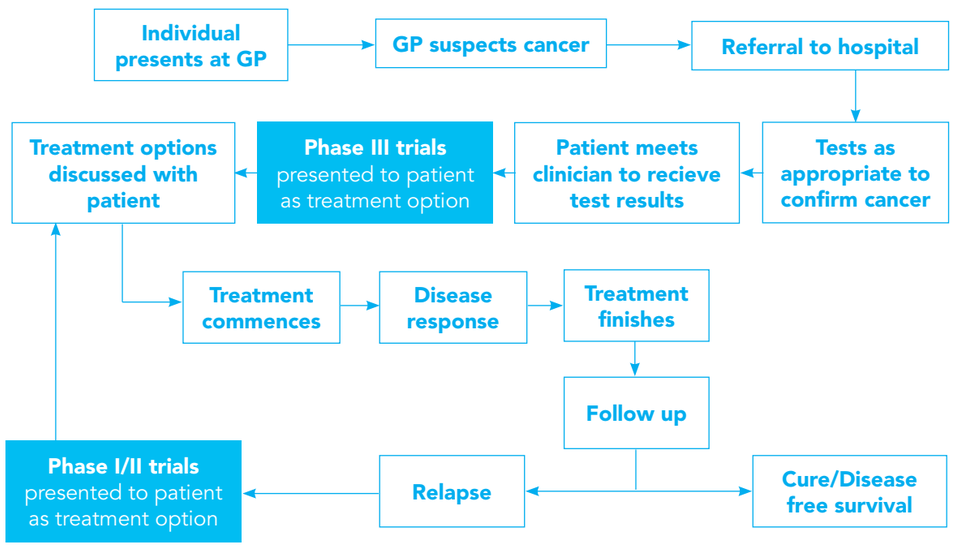
The diagrams below show where Phase I trials fit into the research process and the patient journey.

These diagrams represent the traditional process of early phase trials, although as you will learn at the training day, the nature of trials and the patients taking part are changing.

New treatment journey



A 'typical' patient journey and where the different phases of trials fit in



Clinical development of a drug and a clinical trial protocol

Drug development

There are three key elements to drug development:

1. Testing in computer modelling or human cell lines
2. Animal testing
3. Clinical trials.

This section will focus on the first two elements, exploring what has happened to the drug before it has reached the clinical setting and how the information gathered influences the development of the clinical trials protocol.

Cell line and computer modelling

Human cell line models are used to predict clinical response, generate pharmaco-genetic hypothesis and identify novel mechanisms of action. Work done through computer modelling and cell line work aims to answer initial questions and reduce the number of animal experiments required.

Animal testing

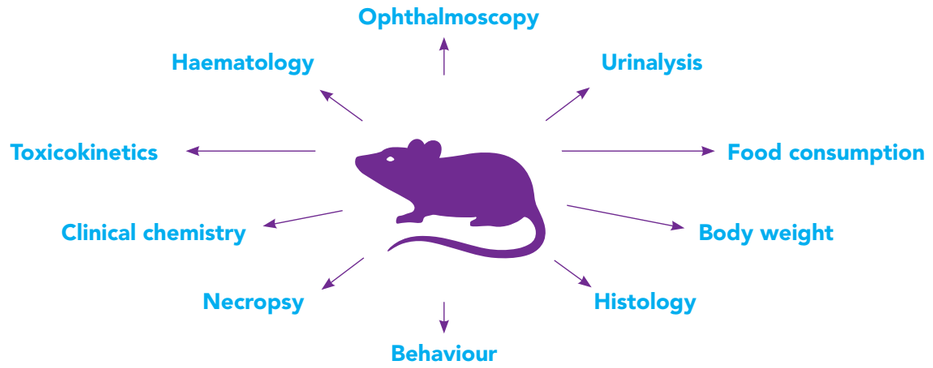
The purpose of animal testing is to test the potential safety and efficacy of the novel agent as their physiology is similar to human's, which gives an indication of how the human body will react or respond to the new drug. Current legislation requires that all new drugs are tested on animals. Cancer Research UK only supports research involving animals when there is no alternative. Further information on their position in relation to this can be found on their website: **www.cruk.org/our-research/involving-animals-in-research**

Animal testing is similar to a Phase I study, in that it starts with a low dose of drug being administered and then the animal is assessed for side effects. Once safety at that dose has been established, a higher dose is administered and again observed until a maximum tolerated dose is identified. Alternative dosing strategies will then be explored.

There are four questions answered by toxicology:

1. Does it damage DNA?
2. Does it damage animals?
3. Does it damage reproduction?
4. Does it damage where it is applied?

These assessments will include evaluation of the many aspects of the animal including:



Animals are subject to some similar tests to those encountered by Phase I patients. Pharmacokinetic (PK) samples are collected to analyse the drug activity. Pharmacodynamics (PD) samples are collected to explore proof of mechanism: does the compound bind to the target; proof of principle: is there a biological change associated with the disease and mechanism of action; and proof of clinical concept: does the drug result in a clinical change on an accepted endpoint in disease, e.g. overall survival.

This preclinical data is used to determine the starting dose, how rapidly to increase the dose, which dose may work and at which dose toxicity may occur. It will also inform any potential risks such as cardio toxicity, tumour lysis syndrome etc.

Initial PD results will determine which biomarkers are suitable for use during the clinical trial. These can include histology, FACS/flow cytometry, circulating tumour cells, circulating hormones, skin biopsy, hair follicle, gene expression and proteomics.

Correct collection of samples is fundamental to the output from the study. The clinical trial lab manual will direct how the samples should be collected, handled and stored.

Drug development

Once an agent has been identified as suitable for trial in humans, formulation and delivery method of the Active Pharmaceutical Ingredient (API) is identified. The agent will undergo a series of tests including solubility of the drug, assessing if excipients are needed to aid uptake within the body, reproducibility and purity checks, and finally stability data to direct storage requirements and delivery timings of the formulated drug. From this work the Investigational Medicinal Product (IMP) is determined and the frequency of dose, route of administration, expiry times and storage conditions are established.

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.

Clinical trial protocol development

With the potential dosing schedule and toxicity determined, primary, secondary and tertiary end points need to be identified. The potential end points and measurements are outlined below:

Primary Objective	Endpoint
Propose a recommended Phase II dose by: Assessing the toxicity and safety profile of the IMP.	Document and determine causality of Adverse Events (AE), Serious Adverse Events (SAE), abnormal laboratory parameters etc.
Establishing the maximum tolerated dose of IMP at planned route/schedule.	Determining a dose at which no more than one patient, out of up to six patients at the same dose level, experience a highly probable or probably <IMP> related dose limiting toxicity.
Or: Establishing the Biologically Active Dose (BAD).	Decrease of <x> % of <x marker> in <x> % of patients Decrease of <x> % of <x marker> in <x> % of patients and there is a plateau in activity in two dose levels (i.e. <x>% absolute difference).

Secondary Objective	Endpoint
To investigate the pharmacokinetic (PK) behaviour of <IMP> in man.	Determining the correlation between PK studies and toxicity and/or efficacy. Include measures wherever possible.
To investigate the pharmacodynamics (PD) behaviour of <IMP> in man.	Determining magnitude and duration of effect of biomarkers following <IMP> administration. Include measures wherever possible.
To document possible anti-tumour activity in patients.	Any/percentage/numbers response (stable disease, partial response or complete response) in any of the patients as determined by the Response Evaluation Criteria in Solid Tumours (RECIST). Time To Progression (TTP) and Progression Free Survival (PFS) may also be used as endpoints for examining possible anti-tumour activity, calculate baseline data according to disease response criteria e.g. RECIST or indication specific criteria. Overall survival should be calculated from the date of first study-related treatment which should be defined for each study in discussion with the Chief Investigator (CI). Usually this is first dose of IMP but this may be first intervention or first dose of non-IMP if this will precede first dose of IMP. You could refer to disease assessment section for details of calculation of endpoint.

Tertiary Objective	Endpoint
To explore the use of <imaging modality or laboratory assay> as biomarkers for detection of early tumour response.	Determining the magnitude of change in <imaging parameter or laboratory parameter> calculated from <imaging modality or laboratory assay> data and the uptake of <tracer or compound> by tumour tissue quantified by <imaging modality or laboratory assay> during the first cycle of <IMP> treatment and their relation with response.
To characterise mutation expression to identify predictive biomarkers of disease response to <IMP>.	Correlation of anti-tumour activity with the expression of clinical relevant mutations including <xxx>.

Phase I clinical trial design

The most common design for first in human trials is the **3+3 design**. Three patients are treated at each dose level. If none of the patients have a Dose Limiting Toxicity (DLT), three patients will be dosed at the next dose level. If one patient has a DLT, three additional patients will be dosed at that level. If no additional patients have a DLT, continue to next dose level. If at any point two or three patients have a DLT, dose escalation is stopped. Three additional patients will then be dosed at the DLT minus one dose level. This is continued until the Maximum Tolerated Dose (MTD) is identified. The use of single patient dose levels in the initial stages of these studies is becoming more common, as this allows for a more rapid progression through the very low doses where efficacy and significant toxicity is considered unlikely.

Rolling 6 trial design is similar to the 3+3 design, in that up to six patients can be enrolled at any dose level. However continuing to recruit patients and not wait for toxicity or the read out of previous patients allows the trial to recruit and complete more efficiently. In a 3+3 design, delays in progressing through each dose level may occur when patients do not complete the DLT period. Whereas the rolling 6 design means that this is achieved in a more timely manner. It is likely that approximately three more patients will be recruited over the course of a trial.

Some Phase I trials are using the two stage **Simon's** design. This is where moving from Phase Ib to Phase II trial only occurs if set criteria are met. The aim of this design is to limit the number of patients treated with an ineffective drug.

With the move towards personalised medicine, where individual genetic mutations are used to direct trial options, umbrella trial designs may feature Phase I drug arms that often follow one of the above designs.

The list of trial designs above is not exhaustive but covers the main designs seen within Phase I cancer research. Each protocol will explain the trial design and why that approach has been selected. There is commonly a trial schema within the protocol which visually explains the design.

Historically, all Phase I cancer trials recruited patients from all solid tumour types. Due to the advances in scientific knowledge and the ability to target specific pathways and mutations, it is now common to have Phase I trials that target a specific patient population, therefore recruiting only patients with a specific tumour type. For example, a trial may require a patient to have triple negative breast cancer before they can be enrolled in the study. This has led to some Phase I trials being open across multiple centres with the expectation of limited numbers being recruited at each site. A balanced portfolio of all-comers studies (recruiting patients with any tumour type) and targeted therapies is routine across ECMC sites.

Complex Innovative Design

Complex Innovative Design (CID) Trials are a way of designing clinical trials to utilise adaptive and other novel statistical methods to streamline and advance drug development and inform regulatory decision making. Being able to offer the UK as a place where innovative trials can be run and are supported by regulations and infrastructure delivers a competitive advantage in the research arena.

Adaptive designs allow planned modifications based on data accumulating within a trial. They are designed to answer multiple questions in parallel. This approach promises greater flexibility and efficiency. These efficiencies can include smaller sample sizes, a more efficient treatment development process and an increase in the chance of correctly answering the clinical question(s) of interest.

Such trials can seamlessly merge several phases or evaluate multiple treatments in multiple patient cohorts within a single protocol. Entire trials that would have historically been carried out independently, can now be conducted in parallel within a 'master protocol' (Renfro and Mandrekar Journal of Biopharmaceutical Statistics 2018). It is also predicted that CID trials can offer increased speed to achieve regulatory approvals, resulting in lower costs.

There are challenges to this approach especially for research teams. Running a study with multiple strands in parallel requires both data management and research nursing expertise. There needs to be increased funding to support recruitment and training for these essential staff members. These types of studies incur higher upfront costs in terms of set-up, and so funders need to adjust payment to cover these costs. This is especially true in biomarker driven trials where many patients may be screened and few recruited due to the lack of the biomarker (Office for Life Sciences, UK DOH, September 2018). Recommendations for sharing expertise has also been suggested to develop investigator interest and support them in developing and running their own complex innovative trials.

Some examples of trials or studies which broadly fall under this category are umbrella or basket trials. Definitions of these types of studies can be found in the NIHR Learn e-learning module on Innovation in Trial Design and Study Delivery: **learn.nihr.ac.uk**

Timelines and costings

Average drug development time is approximately 15 years with additional time for regulatory 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. Only 3-5% of compounds entering the preclinical phase will achieve regulatory approval.

Ethical reviews

Following implementation of the Clinical Trials Directive 2001/20/EC, a single opinion by a single ethics committee is required for each country participating in the trial. There are 66 ethics committees in England although only 23 are approved to review Phase I trials recruiting patients. Each committee has 15 members, who are a mixture of experts and lay people. Research nurses may sit on ethics committees as experts and observers are welcome to attend committee meetings. If you wish to attend, contact the administrator for the individual committee. Details of the committees are available on the HRA website: **www.hra.nhs.uk**.

The ethics committee is required to review the proposed clinical trial and consider the following:

- Relevance of trial
- Trial design
- Risks and benefits
- Protocol
- Suitability of the investigator and supporting staff
- Investigator brochure
- Quality of the facilities
- Subject information (e.g. Patient information sheets, diary cards, alert cards)
- Consent procedure
- Justification for including minors or adults unable to give informed consent
- Insurance/indemnity
- Rewards or compensation for investigators and subjects (rare within cancer research)
- Subject recruitment.

In addition, the ethics committee will also routinely review:

- Confidentiality and data protection
- Retention and future uses of tissue samples
- Sub-studies (e.g. genetics)
- Radiation exposure
- Arrangements for notifying other health care professionals
- Criteria for subject withdrawal
- Criteria for early termination
- Data monitoring arrangements
- Exit strategies and continued care of subjects outside trial
- Patient/public involvement in trial design
- Publication/dissemination of results
- Sponsorship arrangements (including legal representative if sponsor based outside EEA)
- Sources of funding.

Following electronic submission of the valid application to include a complete document set (Covering letter, EC application form, Annex 1 form copy, Protocol, Investigator Brochure, Subject information sheet(s), Consent form(s), List of sites and investigators, CV of Chief Investigator, Evidence of insurance/indemnity, Advertising material*, Subject invitation letter*, Letter to clinician*, Questionnaires*, Patient diary*, Patient card*) an opinion will be given within 60 days or 90 days for gene therapy. If a 'provisional opinion' is given with a request for further information, the Chair or a sub-committee may issue the 'final opinion' following receipt of the information. Application for ethical approval is routinely sought at the same time as the other regulatory approvals required prior to recruitment into a trial.

For more information about the regulatory process, please see the Health Research Authority website: **www.hra.nhs.uk**

*If applicable.

Preparing to run a trial

There has been activity running in the background that you may not be aware of, so here is a brief summary about what may have already taken place.

Feasibility

This is an enquiry usually sent to an investigator or network manager by a Pharma company to see if there is any interest in running a trial, and to determine if the appropriate infrastructure and resource exists to recruit and run the trial.

The feasibility questionnaire contains questions about numbers of eligible patients (be realistic, many investigators overinflate the numbers), R&D department processes (how long do approvals take), amount of experience in the team (PK sampling and other skills), external departments (radiology, laboratory, opthamology, cardiology, nuclear medicine) and pharmacy capacity.

The investigator will be asked to sign a confidentiality and disclosure agreement (CDA). This is a legal agreement between a minimum of two parties which outlines information the parties wish to share with one another, but wish to restrict from wider use and dissemination.

If the feasibility questionnaire sounds positive and the site would like to be considered then a site qualification visit (SQV) is usually arranged.

A SQV involves meeting the team; including the investigator, data management, nursing and pharmacy members. It also involves a look at the facility; treatment areas, emergency equipment, laboratory facility, freezer bay and pharmacy facility.

If the SQV has been successful, you have been selected as a site and this is where the work really begins.

There is a regulatory process that must be followed and there are a number of agencies involved.

Clinical Sponsor applies to the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA issues a Clinical Trial Authorisation (CTA) for Investigational Medicinal Products (IMP).

Other approvals are also required and include submission to a regional ethics committee and local research and development. Please note there are different systems in Scotland and England, due to the differences in legal systems.

The National Institute for Health Research (NIHR) has produced the Clinical Trials Toolkit which is an interactive colour-coded routemap to help navigate through the legal and good practice arrangements surrounding setting up and managing a Clinical Trial of an Investigational Medicinal Product (CTIMP): **www.ct-toolkit.ac.uk/routemap**

Trials teams generally are informed about a pending trial once a finalised protocol has been released and during the time the regulatory approvals are being obtained. This gives a team the opportunity to review the protocol and address questions that can be asked at the site initiation visit.

Protocol

The protocol is the document that guides the entire study. It is important to know the outcome measures, inclusion and exclusion criteria, assessments that are due at each study visit, and confirmation of response criteria. For the research nurse the drug administration section will guide in determining how long a treatment session might last and how many treatment visits are included in a cycle of treatment. The protocol also gives the investigator and pharmacist the information to guide in the writing of the master prescription.

Once the protocol is available, start looking through it and highlight what's important in regard to running the trial. This can be an ideal time to begin to consider trial specific nursing checklists to assist you in collecting data at patient visits.

Being familiar with the protocol allows the team to be able to establish the study intensity, the team's capacity to manage the numbers of patients they are contracted to recruit and determine service implications for pharmacy, the treatment delivery service, and external departments like the lab and radiology. Understanding the protocol allows a trials budget to be produced, considering things like number of patient visits, nursing time, and additional investigations.

You will want to consider what patient group this study is for and know what the study aims, objectives and outcomes are, as well as the number of patients that you will be able to recruit to the study and where they will be identified from.

By studying the protocol you will be able to identify what implications there are on the service and begin working through the practicalities of implementing the study into the hospital environment.

Consider the following:

- Implications on research nurse's time, shift patterns and experience
- Time and resources on the pharmacy department
- Additional chair space and time in the chemotherapy ward
- Extra follow-up appointments in the oncology clinics
- Implications on the external departments with additional trial specific procedures
- Additional training needs for you and the research nurse team
- Do you have enough staff to accommodate the study?
- What equipment is required and ensure it is available
- Anything that's unfamiliar or different from routine care.

Once you have a feel for the trial you can start to think about some of the implications in a bit more detail. Take the protocol, mark it up, highlighting sections that are important to you. **It is important to always check the version number and dates to ensure that you are using the correct protocol.**

Site Initiation Visit

The site initiation visit (SIV) happens just before the study will open and be ready to start recruitment. They are sometimes not held until the regulatory approvals are in place and the site is ready to open and has been given the green light.

Depending on your place of work will depend on who organises the SIV, it may be you as the study nurse. The people who need to attend include:

- Principal Investigator
- Sub Investigators
- Research Nurse
- Pharmacy
- Trial Administrator
- Data Manager
- Laboratory Manager
- Anyone else who will be allocated duties on the delegation log.

The study team will visit you at your site, it is beneficial to allocate yourself as much time as possible to attend the SIV and to have a good understanding of the protocol before the SIV, so you can take any questions and queries to discuss them with the study team.

The study team will have a slide set, handouts and the most up to date protocol. During the SIV, the study team will go through the background of the trial, study design inclusion and exclusion and protocol requirements, what is expected of you as a site and your team's responsibilities.

They will discuss your site approval, all study assessments and requirements, and your processes including source data and capture and any potential amendments. They will also need to look at your site files and ensure that you have all that is required to recruit your first patient.

Patients

Consider the following:

- Patient population
  - How easy will it be to recruit patients?
- Time frame to identify and recruit patients to the study
- Screening
  - This is an effective way to identify potential patients although it can take considerable time
  - Where will patients be identified from?
- Attending Multi-Disciplinary Team meetings – new patients are discussed at these meetings and suitable trial patients can be found.

Posters can be used to advertise the study to patients in the clinic, provided it has received the necessary R&D approval. Emailing colleagues about the study and circulating newsletters are some of the other ways of identifying potentially eligible patients.

Treatments

Looking at the protocol it's good to see what treatment options are available to patients. Is there a time frame for study entry and what is the design? Is it randomised or blinded and if so how will that effect planning the delivery of treatment and care?

Consider the following:

- How often are their treatments?
- How long does the treatment take to administer?
- How many cycles are they to have?
- What's their follow-up schedule like?
- How much chair time is necessary for each treatment?
- When is the completion date?
- What safety bloods are required before, during and after treatment?
- What system is in place to support and protect patients outside of normal hours?

By answering these questions you'll be able to start planning how to integrate the patient's treatments into the research facility/department.

Staff

Having suitably qualified staff to work on the study is essential. Consider the following:

- Who will do what?
- Are staff in the team suitably qualified to fulfil study procedures?
- What specific training is required?
- What supervision will be given to junior staff?
- Is everyone up to date with their GCP training?
- How labour intensive is the trial?
- Are staff familiar with running similar types of studies or is this something new?

Equipment

What additional equipment is required to conduct the study? Many sponsors will supply specific equipment if required and it's important to make yourself familiar with this before you start recruiting patients. Consider the following:

- Trial specific ECGs are fairly common, the sponsor will usually supply these but check who will service and repair them
- Trial specific equipment i.e. patient electronic diary, ensure that you are trained how to trouble-shoot and that a helpdesk contact is provided to patients
- Other specific forms of monitoring equipment may be required but not supplied and it's important they know what your site uses and if it meets their specifications
- Calibration certificates of all equipment used on the study should be readily available and stored in the study site file
- Consider if there are any additional costs for extra equipment/consumables and if so find out who pays for these
- Each study often brings extra trial specific equipment/consumables so think about where it's going to be stored and how it can be made easily accessible when the time comes
- Utilise a stock control system to know when kits and tubes expire and need to be replaced
- If it's trial specific then make sure it's clearly labelled for trial use only and is not used routinely
- Make certain that if you receive a piece of equipment specific to the trial (e.g. a pump) that it is checked by your department that confirms electrical safety (i.e. medical physics) and is legal for use in this country. It requires a CE mark which indicates it is safe for use in the UK. Also ensure that you have training certificates for the use of this pump if it is not standardly used in your facility.

Pharmacy

Consider the following:

- Identify the main pharmacist who will support the trial.
- Who will supply the IMP?
- How and when will it be supplied?
- Is stock sent in advance or as each time point is reached?
- Where will study drugs be stored?
- What documentation do they have?
- Have they received a pharmacy site file and who will manage this?
- What's the expiry time/date of the study drug and is this realistic?
- What happens if the expiry time is exceeded?
- How long will it take to make up?
- Who will reconstitute or prepare the IMP; pharmacy or study nurse?

Notes

Running the trial

When running an early phase trial, you need to be aware of, and be able to balance, the needs of patients and of the protocol. You will have responsibility for screening, recruiting and caring for your patients, but you will also have responsibility to ensure that their care is delivered as per the trial's protocol, and that data is collected as required. You will be expected to communicate with specific clinical trial teams, notifying them of any change of staff, responding to requests for information on your site, and maintaining communication about patients on their clinical trial. In addition, you will also need to be able to respond appropriately to any unexpected events. Managing all of these elements is what makes being an early phase research nurse so challenging and rewarding.

Novel therapy/First-in-Human trials/First-in-Child trial

The development of anticancer drugs has changed from the serendipitous discoveries of the past, to today's purposeful targeting of cancer cells which takes advantage of novel technological developments and a greater understanding of tumour biology. The aim of these new treatments is to affect the essential function of the cancer cell while sparing normal cells and limiting side effects.

The first trial of an IMP in humans is usually a trial of single doses given in increasing amounts. The aims are to assess the tolerability, safety, pharmacokinetics and, if possible, the pharmacodynamic effects of the IMP, and to compare the results with those from the preclinical studies. Novel treatments and treatments that are being used for the first time in human subjects are an unknown entity and safety is the paramount concern in executing these types of early phase trials.

The majority of first-in-child studies will have already been explored in adult trials. In most cases the dose in dose escalation studies with children will be 80% (or below) of the adult recommended Phase II dose. The main aim in first-in-child studies is determining the toxicity profile, the recommended Phase II dose and the optimal dose scheduling of the new drug in children. The safety surrounding these studies mirrors that of first-in-human trials as the unknown entity of the effects of the treatments in children remains a concern.

Screening

Once patients have been identified as potentially eligible for participation in a study, they will have their specific eligibility checked at a screening visit, or visits. Developing close relationships with your medical colleagues is vital to ensure you are able to screen as many eligible patients as possible. The clinical trial protocol will provide you with details of who is eligible for screening as well as the study specific screening requirements and the timeframe for completion. For early phase trials, the screening criteria is often lengthy and specific. It may be that for some patients there will be a requirement to have an additional biopsy or blood test before you are able to screen their eligibility for the main study. Your role as a research nurse is to guide patients and their families through this pre-screening consent process which can be stressful for them. Screening procedures for an early phase clinical trial can be more complex than in later phases of research. The patients may have failed to respond to all conventional treatment options available to them and great sensitivity is needed to ensure they are fully informed and have realistic expectations at this point, as there will be a number of patients who will be ineligible for what they have perceived as 'a last chance'.

The screening registration process may involve registering the patient with the relevant trial office to ensure a slot can be reserved, this is important as it can sometimes take up to 14 days (or longer) to complete the required tests and procedures needed to determine someone's eligibility for a clinical trial. A Screening Number (SNO) may be issued for you to use on patient identifiable data, especially in clinical trials where repeat biopsies of a tumour are required, this does not mean the patient is automatically on the trial but that their details are registered and a slot on the trial is being held for them. For many clinical trials the SNO should be obtained from a pre-defined list of Screening Numbers on the Patient Screening Registration Log which can be found in the relevant clinical trials investigator site folder.

Slot allocation

Each cohort of a clinical trial has a certain number of patient 'slots' that are allocated to the participating sites. The process by which slots are allocated can vary by type of trial, sponsor etc.

Slot allocation in early phase trials can be highly competitive, depending on the recruitment design so it is important for early phase nurses to understand the process for slot allocation in the studies they are running. It is also important that patients understand that even if they are eligible for the study after the screening visit, there is still the possibility that they may not be able to receive the drug. Supporting patients in this situation is an important, and often unrecognised, part of the research nurse role.

Recruitment

Recruitment is a key responsibility of research nurses. Recruitment targets will have been discussed at the site selection visit (see previous section). As research nurses we are patient advocates, and need to ensure that patients are given the information they need before they decide whether to take part in a clinical trial. This is particularly relevant in early phase trials where the aim of the trial may be drug action and safety rather than therapeutic benefit.

Patients must be recruited of their own free will. They should not be made to feel obliged to take part in a trial, nor should they suffer in any way if they do not take part. Additionally, they should be recruited only if they:

- *are capable of giving valid consent, and*
- *have been fully and properly informed so that they understand:*
  - the nature and purpose of the trial
  - any risks, either known or suspected, and any inconvenience, discomfort or pain that they are likely to experience
  - that they can withdraw at any time and without giving a reason
  - that the investigator may withdraw them at any time if they do not follow the protocol or if their health is at risk.

From the ABPI Guidelines for Phase I clinical trials [2018 edition].

These guidelines for research with adults, apply equally to children. It is important to remember that the child is the participant, not their parent or guardian and so ethics principles about consent should always apply to the child participating in research. The research nurse should recognise the need to adapt methods for seeking consent to the child's level of understanding and competency.

Each clinical trial office will produce recruitment reports for all of the sites taking part in a specific trial which may be included within trial newsletters. Look out for this information and share your success across your site, remembering all members of the team including pharmacy that have a role in recruiting eligible patients into the trial at your site.

Sample collection

Sample collection is an important and necessary part of early phase research. Specimens are critical to cancer research because they contain biological information which can be used to characterise cancer cells. They can be used to help us improve our understanding of how diseases start and progress, in diagnosing disease, and in development of new treatments or new screening tests. Many early phase studies use these samples to understand, or predict, benefit (or lack of) from a trial treatment. For example, two patients with similar disease pathology may take part in the same trial and be randomised to exactly the same treatment. The first ends up with a partial benefit to treatment while the second gains no benefit from the exact same treatment. It is only by studying the biology of the disease and the genetic make-up of the individual patients that we can hope to find the answers.

Samples come in many formats, and similar samples stored in certain ways can have numerous names. Blood samples are often broken down into different components including serum, plasma and buffy coat etc. Cancer tissue, sometimes taken by biopsy, is often referred to by the way in which it has been processed. For example a tissue biopsy that has been put in formalin and then into a wax block can be referred to as Formalin Fixed Paraffin Embedded (FFPE), embedded or simply tissue blocks. Tissue that has no 'solutions' added, but is simply frozen down (snap freeze) and required for each study, for example in liquid nitrogen, may be referred to as fresh tissue or fresh frozen tissue. Other common samples that may be taken include urine, faeces, hair, nails and saliva, but this is not an exhaustive list. Only by checking the protocol and lab manual can the research nurse determine the full extent of the sample collection and process required for each study.

Top tips in sample collection and processing

- Read the protocol and lab manual before agreeing to take part in the trial (not something nurses are often asked to do) to ensure that what is being asked is feasible. It's no use agreeing to collect and centrifuge samples within 10 minutes of the blood sample being taken when the nearest centrifuge is 15 minutes walk away.
- Ensure you have the correct equipment available. Some samples need to be spun in a temperature controlled centrifuge but not all centrifuges have temperature control.
- Ensure you have had training in collection and processing. Don't be afraid to say you don't know how to do something. Samples processed in the wrong way can't be analysed or worse still will give the wrong results. Terrible for the study and even worse for the patient who has gone through the procedure of donating the extra blood or tissue sample for nothing.
- It's OK to ask patients for extra samples – don't just assume they won't want to go through an extra procedure. Work done by the ECMC Research Nurse Network Group with patient advocates proved 'it's OK to ask – we can always say no'.
- Stick to the protocol but if you have to deviate make sure you record accurately. Many samples are used to work out how much of a drug is in the patient's blood. This will change from minute to minute, so, if a blood is supposed to be taken at 10 minutes and you take at 12 minutes there will be a difference in the results. You can't stop a patient urgently needing the toilet at the exact time you need to take a sample but you can (and must) record that the sample was taken, for example, 4 minutes later than expected.
- Don't overfill tubes. Liquids expand once frozen and fully filled tubes will either crack or shatter making the sample worthless.
- Plasma and serum look identical to the naked eye but are very different. When aliquoting (moving liquid from a larger tube to multiple smaller tubes) make sure you mark-up individual tubes or you may forget which is which.
- Be honest with any mistakes. It's far better to take a sample out of analysis that you have accidently taken at the wrong time or spun at the wrong speed than to get erroneous results in a study. Rubbish in = rubbish out.
- Keep yourself safe. We are nurses, not lab technicians, and this may be your first time in a laboratory or processing unit.
- Samples are important and so are you. Make sure you understand what is being asked of you and that you feel confident, and competent to carry out the tasks.

Data capture

Data collection for clinical research involves gathering variables relevant to research hypotheses. These variables (patient parameters, data items, data elements, or questions) are aggregated into data-collection forms called Case Report Forms (CRFs) for study implementation.

There is more demand on the timing of data capture on early phase trials as sponsors are asking for a five-day turnaround. Always take time to double check information before sending things onto the trial office. Common areas for mistakes are entering a patient's date of birth instead of their clinic visit, leaving areas blank which will unfortunately result in a query being raised by the trial office.

As patient safety is of primary importance, the sponsors will hold regular safety meetings and in order to analyse data for the Data Monitoring Committees (DMC), there may be a data lock imposed. You will be asked to complete specific areas of CRFs (paper or electronically) by a certain time point. These will be priority sections to complete and return in order for them to review the safety of the trial as a whole. A key consideration for research nurses is to ensure that the data is captured in the most timely way and the development of proformas or worksheets based on the protocol ensures that the data is captured at the right time point.

Drug supply

Due to the nature of the IMP/novel treatments being used, lots of considerations need to be made with regards to the drug supply. Involving your clinical trial pharmacist in team meetings will help to ensure the clinical team are communicating about potential patients and you will be notified of any potential drug supply problems. Take time to find out what the arrangements are locally within your clinical trial pharmacy department, as clinical trial prescriptions may take longer to make and there may need to be additional training for pharmacy staff. Your clinical trial office will be able to help with this.

Pharmacy

Consider the following:

- Storage facilities
- Does the product need to be stored away from daylight?
- Is it to be stored frozen?
- Does the product require processing in a different manner i.e. a novel therapy using a virus?
- How will the product be transported from the pharmacy to the treatment area?
- Will the IMP be reconstituted by the pharmacy or study nurse?

Caring for a patient on an early phase study

Traditionally Phase I treatments involve the administration of sub-therapeutic doses of new agents to healthy volunteers. In contrast, the haemato-oncology Phase I setting differs as we offer real therapeutic options for patients who often have refractory cancers or are at high risk of relapse. In the haemato-oncology setting this leads to an increased responsibility on the research nurse to help guide the patient through the confusing world of not only cancer but also the complexities of research.

An effective early phase research nurse will have a comprehensive understanding of cancer care and build upon that to ensure that their patients are cared for psychosocially. The International Conference on Harmonisation for Good Clinical Practice (ICH GCP) standards emphasise that the protection, safety and wellbeing of trial participants must be a priority. The World Medical Association developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects and stipulates that participants' health and wellbeing must take precedence over all other interests.

Below are a few examples of where we have a key role as advocates for our patients and can use our knowledge to support our patients during this confusing and testing time.

Ensuring informed consent

Phase I cancer patients who are referred are frequently in a time of desperation, often willing to sign on the dotted line without hearing the full extent of what is being asked of them. As their research nurse you are poised to help them understand the true impact a demanding Phase I visit schedule may have on their life and the reasons and rationale for all the tests and visits, for example 'visit one will need 30ml of research blood'. What is the significance of these bloods? How do these research bloods differ from the standard of care bloods? Also for consideration at this time; does the patient have realistic expectations? Does the patient have a good understanding of what is expected of them? Do they have any misconceptions about what it is to be on a trial or have trial treatment? Are they aware of the palliative options or other treatment options available to them? Addressing all of the above will ensure consent is fully informed and the patient is aware of the expectations from the offset. It will also set the foundations for an effective nurse: patient relationship.

It is important to remember that children involved in research require special protection because they are less likely than adults to be able to express their needs or defend their interests. Competence to consent is considered not to depend primarily on age, but rather an ability to understand and weigh up options. Children may not have the capacity to consent but are able to assent to decisions about participation. Assent must be obtained in addition to the consent of the parent or guardian whenever possible.

Sign posting

Phase I studies in cancer have changed in recent years. With the advent of new less toxic targeted agents, patients are actively seeking early phase clinical trials themselves. This can be a frustrating process for the individuals and they are often left floundering. As a research nurse we can help guide this process by engaging with the patient's oncologist, who may not be aware of the individual's desire to find out about experimental treatment, and direct them to other more clinically or geographically appropriate sites. These self-referrals or enquiries must be handled very delicately. This is an opportunity to sign post and ensure that patient choice is upheld. However, a formal referral from the current oncologist will be needed before the patient can be seen.

Managing adverse events

As nurses, we are often the ones that the patient will disclose adverse events to that they 'didn't think were important'. We are poised to collect this valuable information and feed it back and are often the ones helping to unpick what is related and unrelated. This is imperative not only from a patient safety perspective but also means that the data collected and reported is of the highest quality.

Extended care needs

Phase I cancer patients often come with multifaceted problems and as your relationship builds with your patient and their loved ones they will undoubtedly lean on you for support and guidance. Expert communication skills are vital for the early phase research nurse. Additionally, a good understanding of the wider MDT will ensure that the patient is referred to appropriate professionals to ensure best care.

Notes

End of study

What do we mean by end of study?

- The end of study is defined as the date of the last subject's final visit. The sponsor may also end the study upon confirmation that the primary endpoint was statistically met
- The study may terminate prematurely, either in its entirety or at any study site, for reasonable cause by the study team or the investigator. The study may also be stopped due to safety concerns, or because the trial drug has been deemed ineffective
- We may determine the end of the study as when the patient comes to the end of their time on the study.

Whatever the definition is behind the 'end of study', there will be systems created regarding the follow-up of patients. There are two types of end of study, planned and unplanned.

Planned

All studies have a start, a middle and an end; the expected end of study is determined at the beginning, this could be:

- When the trial has met recruitment figures
- When a patient has completed all the expected treatments and trial visits.

Unplanned

An unplanned end of study is:

- If the patient withdraws
- If the patient is unable to continue due to toxicities
- If the patient becomes too unwell to continue
- If the patient is non-compliant
- If the study closes due to safety issues.

A trial closes when:

- Recruitment figures are met. Once a trial nears completion of recruitment, sites are usually notified of limited slot availability. This is managed with effective communication
- Interim analysis finds unsatisfactory results or if recruitment does not meet targets.

Patients who are on treatment after a trial has closed can sometimes continue on the IMP in a compassionate setting. The scope for this is usually included in the protocol. If it isn't, it is worth checking with your monitor, as you will need to be able to explain to your patients what the post-study arrangements are. Discussions with patients about coming off a treatment that is perceived to be working for them are understandably challenging, so research nurses need to be sure they are aware of opportunities, or not, for compassionate use post study and what the alternatives are.

Protocols identify the pathway for patients when they come to the end of the study, whether this is planned or unplanned, including what data is required and how often is follow-up done and for how long.

Points to consider when reading your protocol:

- Patients have the right to withdraw from a study at any time. If this happens, we need to know if the patient has withdrawn locally, or if they would be happy to participate in the study for the purpose of data collection
- Are you aware of protocol specific reasons as to why a patient should be withdrawn?
- Do any patients that withdraw need to be replaced?
- Are the patients' final visit interventions clearly identified?
- Are we advised on what procedures should be followed prior to commencing new treatments?
- Are you clear about the timing and length of the follow-up (specified time or until progression)?
- How long do we follow up if a discontinued patient has ongoing adverse events?
- How long and how frequently is survival follow-up data required?
- What do you do if the whole study is discontinued?

The following table is an example of end of study data collection:

Activity	SCR	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2-6 Day 1	Final Visit	30-day FU Visit	Maintenance Therapy	Post-Treatment Visits	Survival Period
Informed Consent	•									
Medical and Cancer History	•									
Physical Exam (including weight)	•	•		•	•	•	•	•	•	
Vital Signs	•	•		•	•	•	•	•	•	
12-Lead ECG	•	•		•	•	•	•	•	•	
Performance Status (ECOG)	•	•		•	•	•	•	•	•	
Chemistry/Haematology	•	•		•	•	•	•	•	•	
UrinalysIS	•					•				
aPTT, INR	•									
Tumour Assessments	•				•	•			•	
MRI of the Brain	•									
Adverse Event and Concomitant										
Medication Assessment	•	•		•	•	•	•	•	•	
Randomisation		•								
Dispense IMP		•	•		•					
Chemotherapy			•		•					
Administer maintenance treatment								•		
Survival										•

Look at information contained in the protocol detailing the expected procedures following a patient finishing on a trial. From this information we are able to determine what exactly is required at the 'end of study'.

Familiarise yourself with end of study requirements before you recruit your first patients. Don't wait until your first patient finishes. Data collection at the end of study, whether planned or unplanned, is just as important as during treatment, so be prepared. In addition, coming to the end of a study can be distressing for patients on a Phase I trial, so research nurses need to be able to balance the protocol requirements with the needs of patients.

Monitoring, close out visits and regulatory documentation

- Once the last patient has completed the study, or if the study closes early, communication with the trial team increases. All data entered gets scrutinised, queries increase, documentation gets checked and monitoring visits increase.
- Once the trial team are happy that all the Ts are crossed and the Is are dotted, the communication diminishes and finally the study can be closed out at your site.
- A close out visit is organised by the trial team.
- Once this has happened, the PI signs off all the relevant documentation and the trial team gives the authority for the trial to be archived. At this point we can start to delete the emails. Important communications are copied and filed in the site file prior to this time.

Archiving

The Clinical Trials Regulations and specifically, Regulation 31A of the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, define the archiving requirements for Clinical Trials of Investigational Medicinal Products (CTIMPs). All essential documents should be archived and this includes essential documents held by investigators, sponsors and others involved in the conduct of a clinical trial (including services departments such as pharmacy, laboratories and radiology).

Archiving of the study should be considered before the study is open to recruitment. Your site should have local standard operating procedures (SOPs) covering archiving procedures in your area. Make sure you are aware of your responsibilities in relation to archiving. Increasingly, trials are using electronic records, so be sure you are aware of any specific requirements relating to archiving electronic material. For example, some studies require you to archive a laptop that can read the electronic material.

In brief:

- Once we are given the go ahead, the study can be archived
- All the site files can be boxed up and prepared for storage
- Pharmacy and site files are usually co-located
- The files need to be stored for a minimum of 15 years
- Patient notes need to have a sticker identifying that the notes must be stored for 15 years as these are not usually co-located
- SOPs are devised, directing research departments on correct archiving methods.

The clinical trials toolkit has some clear and helpful guidelines on archiving:
www.ct-toolkit.ac.uk/routemap/archiving/

Impact of end of study on research nurses

Research nurses need to be resilient to deliver patient centred care and meet all the trial requirements. In addition, they also need to be excellent communicators and problem solvers. It is a recognised fact that dealing with serious illness and exposure to multiple deaths can put early phase oncology/haematology research nurses at risk of developing a work related psychological disorder. However, research has also uncovered it may be social and personal stresses outside work and pre-existing vulnerability to psychological disorders which are of greater relevance.

Working with cancer patients is special, the intensity of interpersonal relationships can make you as a nurse feel valuable and worthwhile or it can put you at risk of depleting your emotional resources and burning out. Problems do occur when there is an imbalance between the coping ability of the individual and the demands of the work place, with the demands outweighing their ability to cope. Healthcare professionals will either cope with stressors arising from institutional variables or will not be able to do so and hence feel pain. Be kind to yourself and your colleagues, be aware that working as an early phase research nurse can cause psychological stress and work-related burnout. These can lead to job dissatisfaction, possibly impaired work performance, and lost days at work which impacts on the rest of the team and patients.

Be aware of the warning signs in yourself and your colleagues, and the support you can access whether this be informal, such as coffee and cake with colleagues, or formal such as organised clinical supervision. Do what works best for you!

Identifying signs of stress and burnout is important in getting the right help for you. There is a difference between stress and burnout which often gets confused:

- **Burnout** may be the result of unrelenting stress, but it isn't the same as too much stress
- **Stress** involves too much: too many pressures that demand too much of you physically and psychologically.

Stressed people will still feel that if they can just get everything under control, they'll feel better. Burnout is different, it means feeling empty, devoid of motivation, and beyond caring. People experiencing burnout often don't see any hope of positive change in their situations. If excessive stress is like drowning in responsibilities, burnout is being all dried up. And while you're usually aware of being under a lot of stress, you don't always notice burnout when it happens. When you're experiencing burnout, you can feel helpless. But there are positive steps you can take to deal with burnout and get your life back into balance. One of the most effective is to reach out to others.

The NHS website has some helpful advice, tips and tools on health and wellbeing:
www.nhs.uk/Live-well/

Locally you will also have resources available to you through occupational health departments.

Notes

End of study quiz

Below are a series of questions to encourage you to reflect on the issues surrounding end of study issues for patients, their families and research staff. They could form the basis of a revalidation or reflective discussion.

1 **It is understood that dealing with serious illness and exposure to multiple deaths put early phase cancer research nurses at risk of developing psychological stress.**

a. What are the warning signs to look for in colleagues?

b. When coming to the end of a study what additional stress can you identify for staff?

2 **Working with cancer patients can be intensely rewarding with valuable interpersonal relationships between the patient and staff. What support can you as a research nurse access to help ensure you have enough energy to confront all the problems throughout the course of the trial?**

3 **When supporting colleagues what issues could cause stress at the end of a study?**

4 **Recognising when others need support, which of the following factors do you think are proven to result in high stress scores – tick those you believe are true.**

- ☐ Working as a nurse
- ☐ If you are married
- ☐ Aged 21 – 36
- ☐ 1-10 years research experience
- ☐ Conflict with colleagues
- ☐ Value fulfilment of job responsibilities
- ☐ Working long hours
- ☐ Lack of adequate material/tools for job
- ☐ Problematic patients on study

5 **Objective emotional distance from your patient, do you think this is achievable?**

6 **What strategies can be put in place to help clinical staff when relatives of previous clinical trial patients hang onto the team and repeat visits to see everyone?**

7 **Patients may leave a trial due to a level 4 toxicity (more common in chemotherapy trials), how do you think this affects a) the patient and their family b) the clinical trial staff?**

8 **Taking part in an early phase clinical trial can be a burden on the patient and their carers, what thing do you think will cause this?**

9 **'There is a poor prospect of benefit for patients going onto an early phase clinical trial', is this simply exploiting a vulnerable population?**

10 **Many early phase dose finding clinical trials will use sub-optimal doses in the first few cohorts, patients are full of such hope yet the trial they enter has little possibility of tumour response. Do you feel patients understand and accept this?**

11 **Reflect on supportive measures you have in place in your own clinical practice for patients and their carers/family finishing an early phase trial. What good practice can you share?**

12 **Patient A has been to see the lead investigator in a new novel personalised treatment clinical trial. They have spent time discussing the possibility of a trial that could fix the genetic fault found in their cancer. This makes perfect sense to patient A and their family, who eagerly accept the opportunity, particularly as previous chemotherapy has failed to stabilise the disease. Once on the trial, it is clear after week 6 that there has been progressive disease and they are told by the lead investigator that they will have to leave the trial. They are angry and distressed. Discuss how this will affect the patient and their family and the clinical research team.**

13 **Patient B has completed 4 cycles of treatment before coming off study due to toxicity and disease progression. 3 weeks later they appear at their normal research clinic on the off chance that the research team can help as they feel unwell. The patient clearly has become unwell and requires pain control and hospitalisation, the research nurse sees the patient and refers them to the acute oncology team (AOT). The AOT are at capacity and unable to see the patient, they advise the research nurse that the only option is to direct them to A&E but they are aware that there are already 5 oncology patients waiting to be seen in A&E for hospitalisation. The research nurse is aware of how long the patient will have to wait in A&E and has built a good patient nurse relationship with the patient over time. What do you do think the a) patient b) nurse c) nurse manager will be considering in this scenario?**

14 **Patient C has been on a Phase I study for 2 cycles of treatment and is now receiving CT scan results. You are aware that these show disease progression and you have come with the patient to sit in on the doctor's consultation. During the consultation the doctor mentions another Phase I trial happening within another centre some distance away, you notice the patient seems uncomfortable and reluctant to travel. The doctor tells the patient it is really this other trial at another centre or nothing, and he really does feel the next trial should be considered. Do you agree with the statement Phase I trial vs nothing, what more can be considered? When should it be discussed?**

15 **Patient D, a 13-year-old boy, is currently enrolled and receiving treatment on an early phase clinical trial. The most recent MRI scan shows a partial response however the patient feels the burden of his side effects are too great and wants to stop taking the trial medication. This is in conflict with his parents who want him to continue. How as a research team member do you feel this situation should be handled?**

16 **A child is enrolled onto an early phase trial with competitive recruitment which also requires a positive tumour mutation to be present for inclusion in the study. The child's tumour result comes back positive however the cohorts for inclusion into the study have now closed. What are the implications for this family and how do you feel about this situation as the study nurse?**

17 **The family of a 6-year-old girl want to consent to an early phase trial that requires a 3-night inpatient stay every 3 weeks. The patient however has vocalised that she doesn't want to be in hospital and is very tearful during the consent discussion. What would be the best way to deal with this situation?**

18 **A family has a 10-hour return journey to your hospital to receive trial medication for their 4-year-old every 3 weeks. There are no further treatment options available and the trial medication is keeping the tumour stable but no improvement. The family are exhausted by the impact of travelling to your centre and the disruption to family life and other siblings is overwhelming. What do you feel would be in the best interests for this family? To continue treating or come off trial?**

Glossary

ABPI	Association of the British Pharmaceutical Industry: A trade association for UK pharmaceutical companies.
AE	Adverse Event.
Amendment	A written description of a change to the protocol or supporting documents. All amendments should be submitted to HRA for ongoing HRA approval.
AMRC	Association of Medical Research Charities.
AOT:	Acute oncology team
API	Active Pharmaceutical Ingredient.
AR	Adverse Reaction (also known as ADR).
ARSAC	Administration of Radioactive Substances Advisory Committee: Research studies wishing to administer radioactive medicinal products to human subjects need to obtain ARSAC approval before NHS R&D approval.
ASR	Annual Safety Report: For studies involving the use of an Investigational Medicinal Product, this is the annual report which must be submitted to the MHRA detailing all SUSARs and SARs that have occurred in subjects on that study in the past year.
ATMP	Advanced Therapy Medicinal Products.
BAD	Biologically Active Dose.
BRC	Biomedical Research Centre: topic-focused centre with facilities and research active clinicians/academics/research nurses to run clinical projects.
CA	Competent Authority: organisation approving the testing of new drugs/devices or approving the marketing licences, in the UK this is the MHRA.
CC	Coordinating Centre.
CCF	NIHR Central Commissioning Facility.
CDA	Confidentiality and Disclosure Agreement.
CF	Consent Form (also ICR, Informed Consent Form).
CFR	Code of Federal Regulations (US).
CI (i)	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.
CI (ii)	Coordinating Investigator.
CID Trial	Complex Innovative Design Trial.
CPMS	Central Portfolio Management System: a national system that will enable the NIHR CRN to capture high quality study information and produce a range of detailed reports to help manage and deliver studies. CPMS will replace the Portfolio Database, Industry Application Gateway and interim Industry Tracker.
CRA	Clinical Research Associate: usually a commercially employed person supporting the management of clinical studies, helps with obtaining R&D approval, site initiation, study monitoring and close out.
CRF (i)	Case Report Forms: data collection tools provided by a sponsor on which the clinical trial data is recorded for each participant, such as weight, lab results, symptoms.
CRF (ii)	Clinical Research Facility: hospital-like facility with consulting rooms, standard patient beds, ward medical equipment, research nurses supporting only research
CRF (iii)	Clinical Research Fellow
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 of more of a sponsor's trial-related duties and functions.
CSAG	Clinical Studies Advisory Group.
CSG	Clinical Studies Group.
CTA (i)	Clinical Trials Administrator: person providing coordinating/secretariat support for running clinical studies.
CTA (ii)	Clinical Trials Agreement: contact between the legal sponsor and the hosting research sites.
CTA (iii)	Clinical Trials Associate (similar to CRA): person involved in the management of a study from initiation, through conduct/monitoring to close out.
CTA (iv)	Clinical Trials Authorisation: The regulatory approval for a clinical trial of a medicinal product issued by the MHRA.
CTIMP	Clinical Trial of an Investigational Medicinal Product.
CTU	Clinical Trials Unit: Design and manage CTIMPs, sometimes in specialist clinical areas, such as cancer, or types of trials, such as RCTs.
Delegation of Duties Log	Document detailing who has been delegated each duty by the Principal Investigator.
DH	Department of Health (for England).
DLT	Dose Limiting Toxicity.
DMC	Data Monitoring Committee.
DNA	Deoxyribonucleic acid molecule that carries the genetic instructions used in the growth, development, functioning and reproduction of all known living organisms and many viruses.
DPA	Data Protection Act.
DQ	Data Query.
DSMB	Data and Safety Monitoring Board: An independent committee composed of clinical research experts and community representatives that reviews data whilst a clinical trial is in progress to ensure that participants are not being exposed to undue risk.
DSUR	Development Safety Update Report: In addition to the expedited reporting required for SUSARs, Sponsors are required to submit a safety report (DSUR) to the MHRA and Research Ethics Committee, once a year throughout the clinical trial or on request.
ECG	Electrocardiogram.
ECMC	Experimental Cancer Medicine Centre.
eCRF	An electronic CRF.
Eligibility	A clinical assessment of whether the potential participant meets the inclusion and exclusion criteria for the study as described in the protocol.
EMA	The European Medicines Agency: A body of the European Union which has responsibility for the protection and promotion of public health through the evaluation and supervision of medicines for human use.
EPAP	European Patient Ambassador Programme.
eTMF	An electronically stored TMF.
EU	European Union.
EudraCT	European Clinical Trials Database: A database of all clinical trials in Europe, held since 1994 in accordance with EU directive 2001/20/EC.
FDA	Food and Drug Administration: the Competent Authority in the United States, giving authorisation to conduct clinical trials and issuing marketing licences.

Feasibility	The process of reviewing the protocol to determine whether or not a study can be safely and effectively delivered.
FFPE	Formalin Fixed Paraffin Embedded.
GAfREC	Governance Arrangements for Research Ethics Committees.
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.
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.
GTAC	Gene Therapy Advisory Committee: the ethics committee for clinical studies using genetically modified products; usually no REC approval required.
HEI	Higher Education Institution.
HFEA	Human Fertilisation and Embryological Authority.
HRA	Health Research Authority.
HRA Approval	The process for the NHS in England that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK Health Departments' Research Ethics Service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study.
HRC	Honorary Research Contract.
HSE	Health and Safety Executive.
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).
ICF	Informed Consent Form.
ICH-GCP	International Conference on Harmonisation (Europe, USA, Japan): Defined standards for the terminology, design, conduct, monitoring, recording, analysis and reporting of a study. Section E6 of ICH defines principles of Good Clinical Practice (referred to as ICH-GCP).
IDMC	Independent Data Monitoring Committee.
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 provide advice to help you decide if your product is an investigational medicinal product (IMP).
Indemnity	Compensation for damage, loss or injury.
Investigator	Researcher conducting the (clinical) study, those researchers leading the team are referred to as CI or PI.
IRAS	Integrated Research Application System: A single web-based system for completing applications for the permission and approvals required for health and social care research in the UK.
IRB	Independent Review Boards: US equivalent of authorised REC.
IRMER	Ionising Radiation Medical Exposure Regulations: part of NHS R&D approval, usually done by the local hospital experts.

ISF	Investigator Site File: A file designed for use in organising and collating all essential documentation required to conduct a study in accordance with the principles of GCP and the applicable regulatory requirements (e.g. REC approval/letter correspondence, MHRA approval, blank CRF, staff CVs, delegation of duties log etc.).
ISRCTN	International Standard Randomised Control Trial Number: A simple numeric system for the identification of randomised controlled clinical trials worldwide. Allows the identification of trials and provides a unique number that can be used to track all publications and reports resulting from each trial.
LCRN	Local Clinical Research Network.
LPMS	Local Portfolio Management System: local systems which capture high quality study information and integrate with CPMS.
MCA	Mental Capacity Act.
mCIA	model Clinical Trial Agreement: for IMP studies with commercial sponsor/CRO conducted; standard templates for the UK (use is not obligatory).
MDT	Multidisciplinary team.
MfHU (CT)	Medicines for Human Use (Clinical Trials) Regulations: SI 2004: 1031 and subsequent amendments 2006: 1928, 2006:2984, 2008:941, 2009:1164 and 2010:1882 are the UK Statutory Instruments translating EU directives 2001/20/EC and 2005/28/EC into UK law, laying down the legal requirements for conducting CTIMPs in the UK.
MHRA	Medicines and Healthcare products Regulatory Agency: The UK Competent Authority (CA) and licensing authority for medicines and medical devices.
mNCA	model Non-Commercial Agreement for clinical research studies; standard template for the UK (use is not obligatory).
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.
MRC	Medical Research Council.
MRI	Magnetic Resonance Imaging.
MTD	Maximum Tolerated Dose.
Multi Centre Study	A study conducted according to a single protocol but carried out at more than one site and by more than one investigator; one CI oversees several local PIs.
ND	Not done (in CRFs).
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.
NK	Not known (in CRFs).

NOCRI	National Office for Clinical Research Infrastructure.
Non-substantial amendments	Changes to the details of a study that have no significant implications for the subjects, the conduct, the management or the scientific value of the study (sometimes referred to as administrative amendments).
ODP	Open Data Platform: an online, open platform which provides secure access to collated study and recruitment data.
PD	Pharmacodynamics: is the study of how a drug affects an organism.
PFS	Progression Free Survival.
Phase I/1	Phase I/1 trials are usually small trials, recruiting only a few patients, and their main aim is to determine the safety of a drug. When laboratory testing shows that a new treatment might help treat cancer, Phase I 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.
Phase II/2	Phase II/2 trials aim to find out: • If the new treatment works well enough to test in a larger Phase III 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.
Phase III/3	Phase III/3 trials compare new treatments with the best currently available treatment (the standard treatment). These trials may compare: • A completely new treatment with the standard treatment • Different doses or ways of giving a standard treatment • A new way of giving radiotherapy with the standard way.
Phase IV/4	Phase IV/4 trials are done after a drug has been shown to work and has been granted a licence. The main reasons for running Phase IV trials are to find out: • More about the side effects and safety of the drug • What the long term risks and benefits are • How well the drug works when it's used more widely.
PI	Principal Investigator: The lead person at a single site designated as taking responsibility within the research team for the conduct of the study.
PIC	Participant Identification Centre: NHS or other organisation which only identifies participants from a database etc, but recruitment/receiving consent and study conduct are managed elsewhere.
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.
PSV	Pre-site Selection Visit
QA	Quality Assurance.
QC	Quality Control.
QLQ	Quality of Life Questionnaire.
R&D	Research and Development: often name of department within NHS hospitals giving permission to conduct projects on those facilities with patients/staff.
RCT	Randomised Controlled Trial: A randomised controlled trial (RCT) is 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.

RDS	Research Design Service: organisation with a number of experts who can help write the protocol/documents for NIHR grant applications.
REC	Research Ethics Committee: authorised by HRA to review study documents for research taking place in the NHS, or social services. Some RECs specialise in Clinical Trials, or topics such as research in children, MCA. All research in NHS/ social services must have been reviewed by a UK REC.
RECIST	Response Evaluation Criteria in Solid Tumours: a set of published rules that define when cancer patients improve (respond), stay the same (stable) or worsen (progression) during treatments.
Research Passport	A system for HEI employed researchers/postgraduate students who need to undertake their research within NHS organisations, which provides evidence of the pre-engagement checks undertaken on that person in line with NHS Employment Check Standards (among them CRB and occupational health checks).
RfPB	Research for Patient Benefit: NIHR research funding stream.
SAE	Serious Adverse Event.
SAR	Serious Adverse Reaction.
Screening	The process of identifying eligible patients prior to approaching them to determine if they are willing to consent to participate in the study.
SDV	Source Data Verification: checking the original data record, such as lab reports, patient medical notes against what was transferred onto the CRF/into a database.
SI (i)	Statutory Instruments: document which defines UK law on a specific topic, e.g. how to manage a clinical trial.
SI (ii)	Sub-Investigator (as in ICH-GCP, ICH does not use the term Co-Investigator).
Site	The NHS organisation in which study activities and assessment are performed or the location(s) where trial-related activities are actually conducted. Each site/Trust needs to give R&D approval.
SIV	Site Initiation Visit.
SLA	Service Level Agreement.
SMO	Site Management Organisation.
SmPC	Summary of the Product Characteristics: smaller version of the Investigator Brochure with details on pharmacological effects, but issued for a product that already holds a marketing licence.
SNO:	Screening Number
SOP	Standard Operating Procedure: detailed written instructions designed to achieve uniformity of the performance of a specific function.
SQV	Site Qualification Visit.
Substantial Amendment	An amendment to the protocol or any other study specific documentation, the terms of the REC application or the terms of the CTA application (as applicable) that is likely to affect to a significant degree the safety or physical or mental integrity of the participants or the scientific value of the trial.
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 or the SmPC) and suspected, as it is not possible to be certain of causal relationship with the IMP.
TMF	Trial Master File: file with essential documents held by the Chief Investigator/ Sponsor organisation.
TTP	Time to Progression.
WHO	World Health Organisation.
WMA	World Medical Association.

Useful information

ECMC network
Information about the ECMC network, including details and resources relating to the ECMC Research Nurse Network Group. You can sign up to the Research Nurse Network Group via the ECMC website. If you have any queries about the network please email:
ecmcadmin@cancer.org.uk
www.ecmcnetwork.org.uk

ABPI Guidelines for Phase I clinical trials (2018 edition)
http://www.abpi.org.uk/publications/guidelines-for-phase-i-clinical-trials-2018-edition/

CRUK Excellence in Research Programme
The Excellence in Research Programme is uniquely designed to support clinical research nurses who work on cancer trials with their professional development. Includes education and networking opportunities such as a free online course on Demystifying Targeted Cancer Treatments.

You can find out more and sign up here: **www.cancerresearchuk.org/health-professional/learning-and-support/resources/excellence-in-research-programme-for-clinical-research-nurses**

If you have any questions about the programme, email: **researchprogramme@cancer.org.uk**

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

CRUK Science Updates
Updates on key news in cancer research
scienceblog.cancerresearchuk.org

ECMC Funders
Further information on the ECMC funders:
Cancer Research UK – **www.cruk.org**
National Institute for Health Research – **www.nihr.ac.uk**
Chief Scientist Office, Scotland – **www.cso.scot.nhs.uk**
HSC Public Health Agency, R&D Division, Northern Ireland – **www.research.hscni.net**
Health and Care Research Wales – **www.healthandcareresearch.gov.wales**

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

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 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

Health Research Authority

Information about the regulatory process

www.hra.nhs.uk

Involving animals in research

Information on Cancer Research UK's and the NIHR's positions on involving animals in research

www.cruk.org/our-research/involving-animals-in-research

www.nihr.ac.uk/about-us/policies-and-guidelines.htm

MHRA Good Clinical Practice Guide (Grey Book)

The GCP Guide is a very useful resource for conducting Phase I studies. It is only available as a hard copy.

Reference: Great Britain. Medicines Healthcare products Regulatory Agency. (2012). Good clinical practice guide. London: Medicines and Healthcare products Regulatory Agency: Crown.

NHS Live Well

Advice, tips and tools to help you make the best choices about your health and wellbeing

https://www.nhs.uk/Live-well/

NHS Moodzone

Practical advice, interactive tools, videos and audio guides to help you feel mentally and emotionally better

www.nhs.uk/conditions/stress-anxiety-depression

National Institute for Health Research (NIHR)'s clinical trials gateway

Guidance on how trials work and help to connect your patients to researchers running trials they might be interested in

bepartofresearch.nihr.ac.uk/

NIHR Clinical Trial Toolkit

An interactive colour-coded routemap to help navigate through the legal and good practice arrangements surrounding setting up and managing a Clinical Trial of an Investigational Medicinal Product (CTIMP)

www.ct-toolkit.ac.uk/routemap

NIHR Learn

The NIHR Learn platform is a key part of the suite of learning programmes, resources and communities in support of the Workforce Development Strategy. Includes the Future of Health e-learning course which contains modules on Cell & Gene Therapy and Innovation in Trial Design & Study Delivery.

learn.nihr.ac.uk

Notes

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