



# The Guide to Efficient Trial Management

## Cancer Supplement

*NCRI Cancer CTU Training Subgroup*

# Foreword

This resource was developed for Trial Managers working in oncology, to be used alongside the UKTMN Guide to Efficient Trial Management.

## Acknowledgements

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## Guidance Notes

This document is primarily aimed at trial managers working within an academic CTU, but this resource may be useful to other trial staff whether located within a CTU or at site.

Please be aware that whilst we aim to update the supplement regularly, cancer clinical trials are a rapidly changing field. Please make sure you access the most up to date information available online. Useful acronyms can be found in Appendix 1 and further information in Appendix 7.

We would value your feedback ([h.meadows@ucl.ac.uk](mailto:h.meadows@ucl.ac.uk)). If you would like to be involved in the continuing development of the handbook, please contact one of the editorial team.

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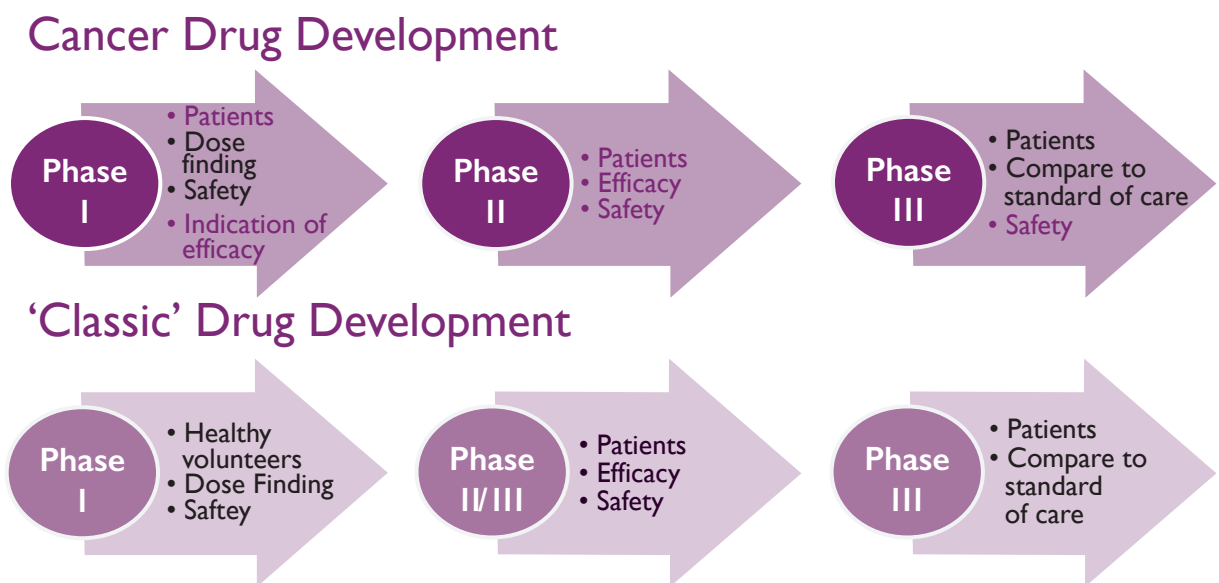
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# Section 1. Understanding cancer trial design

Cancer trials cover a wide range of settings from screening, imaging, diagnosis through to treatment and palliative care and therefore a wide range of methodologies are used. The development of drugs from Phase I through to Phase III differs from other disease areas where initially healthy volunteers are used as the treatment interventions carry a high risk of adverse events. See diagram below.

## 1.1 Cancer drug development

The development of cancer drugs differs slightly to the classic development of drugs described in most books and websites, particularly during early development. In Phase I cancer trials, healthy volunteers are not involved as many of the treatments have serious side effects and can be carcinogenic. Phase I trials include patients whose cancer persists despite all available treatment options or for whom there is no other proven or established treatment that may help them. Because patients with cancer are participating in Phase I trials, tumour response can be monitored to give early indications of efficacy, which is not the case in healthy volunteer trials. Academic Phase I trials may involve using unlicensed drugs, or a licensed drug outside its licensed indication.



### Diagram to show differences between cancer and non-cancer trials

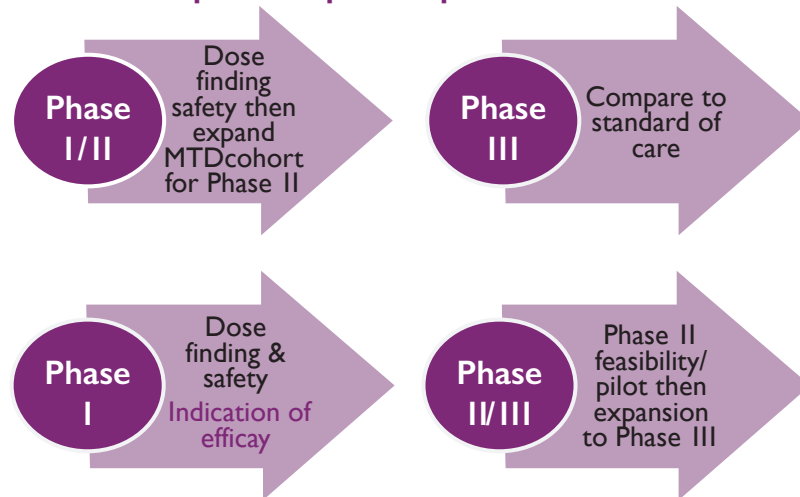
**Blinding and placebos in cancer trials:** Because many cancer interventions are invasive (surgery, radiotherapy, intravenous drugs etc.) placebos are only used when an oral drug is available for use. Even then, due to adverse events (AEs) specific to the drug being investigated, clinicians will not always be blind to the treatment allocation. Placebos may be helpful in identifying the additional burden of AE's in cancer trials, over and above those reported as being related to cancer and other forms of therapy.

**Control group in cancer trials:** The control arm should be the best standard of care which may or may not include active treatment. Active treatments include one or more types of treatment. For example surgery, radiotherapy, drug therapy (single or multiple), or combinations of therapies. If no active treatment is available, the comparator may be 'best supportive care'.

**Seamless designs:** Academic cancer trials often combine 2 phases to achieve results more quickly and efficiently within a single protocol. For example:

- Phase I/II: dose finding initially, expanding into a phase II cohort once the Maximum Tolerated Dose (MTD) has been determined.
- Phase II/III: a feasibility or pilot Phase II trial might be designed to seamlessly move into phase III once feasibility, response and safety have been assessed.

## Can we speed up the process?



Under specific circumstances the need for Phase III trials may be omitted, for example in the case of rare tumours when there are insufficient patients for a Phase III trial. Some cancer drugs are licensed on the basis of randomised Phase II data.

**Non-inferiority trials:** Phase III trials are mostly designed to demonstrate superiority of one treatment arm over another, some are designed to test whether the new intervention is no worse than the standard by more than a small pre-specified amount, called the non-inferiority margin. For example, some new cancer treatments have fewer side effects and the cancer may have an excellent prognosis and therefore the aim of the trial may be to establish “non-inferiority” in terms of tumour response with an improvement in symptoms and /or quality of life.

**Window of opportunity trials:** In these trials there is a window, or gap, between standard treatments or interventions that might be used to test something new or enhance subsequent treatments. For example treatment with a radiosensitiser prior to starting standard radiotherapy or a new drug prior to surgery.

### The changing face of cancer drug development

Factors that can predict prognosis or response to treatment have been used in cancer trials for many years. The increased understanding of cancer biology means that many cancer trials now include prognostic and predictive biomarkers, to select patients suitable for trial interventions.

#### Biomarkers in cancer

**Prognostic markers:** Factors known to be associated with good or poor prognosis (i.e. disease outcome such as relapse or death) irrespective of the treatment received e.g. increasing: stage of disease, invasiveness, poor differentiation, prevalence of P53 mutation, C Reactive Protein etc.

**Predictive markers:** When present these factors are associated with a treatment specific benefit e.g. the following genetic markers

- BRCA mutation & response to PARP inhibitors.
- BRAF mutation & response to vemurafenib.
- EGFR activating mutations & EGFR inhibitors such as erlotinib/gefitinib/Iressa.
- HER2 +ve breast cancer & Herceptin.
- KRAS mutation & cetuximab in bowel cancer etc.
- Oestrogen receptor +ve breast cancer & tamoxifen.

In addition, many drugs are now being developed to target specific proteins and/or important pathways related to cancer formation and growth. This new era means that increasingly novel outcome measures are being used and ‘traditional’ cancer trial design is changing.



## Recent developments in cancer trial design

**Adaptive designs:** Trials in which unblinded data are monitored and used to determine the future course of the trial based on prospectively defined decision rules. This design provides information which leads to better decisions regarding dose, regimen, sample size, target indications and subpopulations in later phases. One type of adaptive design in Phase I trials is the Continuous Re-assessment Method (CRM).

**Platform:** This definition includes a range of designs within a single protocol to increase the efficiency of traditional RCTs. They may include different phases or compare multiple experimental arms, usually against the same control arm, different interventions may be dropped for futility or novel interventions can be added as they become available. Some platform trials are called Multi-arm multi-stage (MAMS) trials and these are another type of adaptive design.

**Umbrella:** Trials in which the patients included have cancer in the same location but with different biomarker mutations.

**Basket:** Trials in which patients have the same biomarker mutation but cancer in different organ types (lung, colon etc).

## 1.2 Patient selection

In order to establish patient suitability for trial entry, patients may experience several interventions in the process of being diagnosed with cancer or being screened to determine if they are at high risk of developing the disease. Understanding these steps and the material and/or data collected can be important when designing a new clinical trial. It is also useful to be aware of the different people involved in cancer care (see Appendix 2).

Eligibility in cancer trials is usually based on:

- **Tumour status:** Location, TMN staging (see Appendix 3), histological type and increasingly trials are looking for very specific patient populations based on specific biomarker results. This can mean patient eligibility may require collecting information from multiple sources in a timely manner, e.g. imaging, pathology, genetic testing, and molecular diagnostics.
- **Fitness for treatment:** Adequate performance status, renal, liver and haematological parameters together with specific checks for different classes of drugs e.g. cardiac toxicity.
- **Ability to measure outcome:** The outcome chosen should be a validated method e.g. EORTC Quality of Life (QoL) questionnaire, Response Evaluation Criteria in Solid Tumours (Recist) criteria etc.

**Tumour status:** Identification and diagnostic Interventions

**Cancer imaging:** For most cancers a GP referral to exclude cancer will result in the patient undergoing some form of imaging to locate potential cancer. There are many different types of imaging available. Which of these is used will depend on the symptoms reported by the patient. Examples of different imaging techniques include X-rays, bone scans, CT scan, Endoscopy, MRI, PET, PET/CT, Ultrasound (US) etc.

**Histology & Cytology:** During, or following imaging, samples of the tumour will be taken and sent to pathology to determine whether the patient's cells are cancerous or benign. Cytology refers to the examination of cells, e.g. from body fluids or obtained via fine needle aspiration. Histology is when the examination is of tissue taken from a biopsy or a surgical specimen.

The results from imaging, pathology and laboratory tests and information on the extent of the disease will be collated (see Appendix 4 for disease terms). The information will be discussed at a multi-disciplinary team (MDT) meeting at which decisions will be made about treatment and trial options.

**Screening programmes:** For some cancers, national screening programmes have been established to try and identify cancer at an early stage, for example:

- National Bowel Cancer Screening Programme:  
[www.gov.uk/topic/population-screening-programmes/bowel](http://www.gov.uk/topic/population-screening-programmes/bowel)
- NHS Breast Cancer Screening Programme:  
[www.gov.uk/topic/population-screening-programmes/breast](http://www.gov.uk/topic/population-screening-programmes/breast)

**Fitness / suitability for treatment: Health status at time of trial entry**

**Laboratory tests:** As for many diseases the patient's health status will be determined using a variety of tests, which in cancer often includes tests to determine the functioning of the patients cardiac, renal and

liver systems. Cancer patients, especially those with advanced cancers, may still be eligible if their results fall out of the normal range as expanded ranges are used when assessing eligibility (e.g. 5x upper limit of normal for liver function tests). Depending on the intervention and known adverse events additional tests may be needed e.g. echocardiogram to assess cardiac function, glomerular filtration rate to assess renal function etc.

**Performance status:** A key indicator of a person's ability to tolerate cancer treatment is a patient's performance status. See Appendix 5 for performance status.

**Tumour markers:** Increasingly tumour markers are being used to select patients who are likely to respond to targeted treatment and exclude patients unlikely to benefit from treatment.

**Stratification factors in cancer trials:** Site variations, patient factors or tumour characteristics that are known, or likely, to influence outcomes (because they impact on prognosis or response to treatment) will need to be balanced between randomised treatment groups. To avoid imbalances stratified randomisation or minimisation is used. The treatment allocation programme ensures the chosen stratification factors are balanced between randomised arms, e.g. site, size or stage of tumour, serum markers etc. Usually up to three factors are used.

### Ability to measure outcome(s):

Depending on the outcome measure additional checks may need to be made to ensure the patient/tumour will be evaluable i.e. it is possible to assess/measure and record the outcome at the required time point (see outcome measures below). For example

- Tumours may be considered non-measurable and the patient may not be eligible if measurable response is the primary outcome.
- If completion of QoL forms is mandated, is the patient able to complete forms?
- Where international participation is planned, will healthcare systems enable collection of long term follow-up data.

### Further information on cancer diagnosis and tests:

- Cancer Research UK (CR UK): [www.cancerresearchuk.org/about-cancer/cancer-in-general/tests](http://www.cancerresearchuk.org/about-cancer/cancer-in-general/tests)
- Macmillan: [www.macmillan.org.uk/information-and-support/diagnosing/how-cancers-are-diagnosed/tests-and-scans](http://www.macmillan.org.uk/information-and-support/diagnosing/how-cancers-are-diagnosed/tests-and-scans)

## 1.3 Treatment interventions

A wide range of interventions are used to treat cancer. Depending on the cancer type and stage, these interventions may be used alone or in combination. See Appendix 6 for treatment terms.

### Investigational Medicinal Product (IMPs):

- **Chemotherapy:** The use of anti-cancer drugs (cytotoxic drugs) to kill cancer cells.
- **Hormone therapy:** A treatment that uses medicines to block or lower the amount of one or more hormones in the body to slow down or stop the growth of cancer.
- **Targeted agents:** Drugs that work by 'targeting' specific differences in the way cancer cells behave (e.g. to prevent the cancer cells from continuing to grow or divide).
- **Immunotherapy:** These drugs use the body's own immune system to fight cancer by helping the immune system to recognise and attack cancer cells.

Vaccines are a form of immunotherapy. They are not yet widely used for treatment, often they are only available through participation in a clinical trial. An example of vaccination for prevention of cancer is the HPV vaccine for cervical cancer.

**Surgery:** In cancer, surgery may be used for many different reasons e.g. diagnosis, treatment, to reduce a person's risk of developing cancer, reconstruction after treatment, to alleviate symptoms of cancer.

**Radiotherapy:** Uses radiation (usually x-rays) to treat cancer. The radiation can be delivered from outside the body (external radiation) or from within the body (internal radiation). There are many different techniques and approaches for the delivery of radiotherapy depending on the tumour type, location and purpose of the treatment. See [www.nhs.uk/conditions/radiotherapy/](http://www.nhs.uk/conditions/radiotherapy/).

- Radical or curative radiotherapy aims to cure the patient.
- Palliative radiotherapy may be used to alleviate symptoms caused by a tumour.

**Advanced therapies (ATIMPs):** gene, cell and tissue therapies; see main guide.

**Medical devices:** see main guide but note the Medicines and Healthcare products Regulatory Agency (MHRA) considers assays as intravenous diagnostic devices and medical devices.

**Novel delivery:** There is increasing research looking at novel modes of delivering treatment, e.g. TARDOX: delivery of doxorubicin chemotherapy in a heat sensitive coating, which can be melted by ultrasound. This delivers chemotherapy to the area localised by ultrasound, thereby minimising toxicity and increasing efficacy.

### Further information on cancer treatments

Useful links for more information on the different types of treatment.

- Macmillan: [www.macmillan.org.uk/information-and-support/treating](http://www.macmillan.org.uk/information-and-support/treating)
- Cancer Research UK: [www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment](http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment)

## 1.4 Outcome measures

### 1. Safety

There is almost always an outcome measure related to safety in cancer trials, irrespective of phase. AEs are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events - NCI CTC AE (current version 5, 27 Nov 2017) which maps to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes.

#### AE grading:

- Grade 1: Mild AE, minimal or no intervention
- Grade 2: Moderate AE, minimal intervention required
- Grade 3: Severe AE, intervention required
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Grades 3-5 are almost always, but not exclusively, SAE/Rs and may or may not be expected for the treatment(s) being investigated.

**Dose Limiting Toxicity (DLT):** This is often an outcome in Phase I cancer trials. This means an adverse event that is either deemed to be unacceptable or has the consequence of requiring a significant dose reduction / stopping the drug, and would limit further dose escalation in a Phase I trial. These usually occur within the first few cycles of treatment.

**Maximum Tolerated Dose (MTD):** This is often the primary outcome in Phase I cancer trials. This is the highest dose that causes a pre-specified level of acceptable toxicity e.g. moderate reversible toxicity in most patients. The MTD is used to determine the dose used in subsequent trials.

### 2. Efficacy

#### a. Tumour response

##### Solid tumours:

**RECIST** (Response Evaluation Criteria In Solid Tumours) criteria is used to measure tumour response and progression, see Appendix 3 for summary information.

- V1.0: Therasse P et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–16.
- V1.1: Eisenhauer EA et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) Eur J Cancer. 2009; 45:228–47.



**PERCIST (PET Response Criteria):** Wahl RL et al. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009; 50 (Suppl 1):122S–150S.

**iRECIST; Immunotherapy responses in solid tumours:** Responses to immunotherapy drugs may not always easily be described by RECIST criteria and therefore different response criteria have been developed. These immunotherapy response criteria are outlined in iRECIST criteria and take into account durable long term stable disease, response following tumour flare etc.

- iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. L Seymour et al. Lancet Oncology 2017 18 e143 - e152.

**Biomarkers for response:** None yet validated in solid tumours.

**Haematological malignancies:** use guidance specific to the type of malignancy.

Lymphomas: see Appendix 3 for further information

- Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014).
- Immunotherapy response: The Lugano criteria have been refined (LyRIC criteria Cheson et al Blood 2016 128:2489-2496).
- Deauville criteria - a 5-point scale, based on the most intense uptake in a PET scan in a site of initial disease, if present, as follows:

1. No uptake
2. Uptake  $\leq$  mediastinum
3. Uptake  $>$  mediastinum but  $\leq$  liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions
- X. New areas of uptake unlikely to be related to lymphoma

A score of 1-3 = typically PET negative and a score of 4-5 = PET positive and typically these patients need to have their treatment escalated.

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus Guidelines of the International Conference on Malignant Lymphomas Imaging Working Group (Barrington et al. 2014).

**Leukaemias:** Chronic Myeloid Leukaemia Response Criteria, Hallek, Blood 2008, 111 (12), 5446-5456.

**Myeloma:** International Myeloma Working Group consensus response criteria, Rajkumar, Blood 2011, 117 (18), 4691-5.

## **b. Time to event outcome measures**

These outcome measures indicate the length of time a patient is free of an “event” of interest e.g. death or disease status. The aim is to determine if the new treatment is more effective at extending the duration patients are free of the event.

For example:

- Overall survival (OS), event = all deaths irrespective of cause.
- Cause specific survival (CSS), event = deaths due to the cancer only.
- Progression free survival (PFS), event = date of progression and/or death.
- Disease free survival (DFS), event = date of disease detection and/or death.

The definitions of outcome measures other than OS can vary, even within the same tumour type. The protocol should explicitly define what events are included in the definition (e.g. are new tumours and cancer treatment related deaths included or not).

**Cause of death:** will usually be reported irrespective of the main outcome measure used. Categories may include death due to index cancer, due to treatment, due to other cancer or non-cancer deaths.

### c. Patient reported outcomes

In cancer trials several standardised, validated, cancer specific and site-specific questionnaires exist to assess a variety of factors important to patients. These questionnaires have clearly defined methods and procedures, ensuring a consistent measurement and allowing comparison of data from different studies.

#### 1. EORTC questionnaires

The core questionnaire (EORTC QLQ-30), has 30 questions covering 5 functional states (see below). There are two final questions covering “overall health” and “overall quality of life” and 3 symptom scales. Disease-specific modules exist for most cancers. E.g. CX-24, which has 24 questions aimed at cervix cancer patients. They are not usually used independently of the QLQ-30. See <http://groups.eortc.be/qol/eortc-qlq-c30>.

- Physical
- Role
- Emotional
- Social
- Cognitive functioning

Answers are graded on a 4-point scale.

- Not at all
- A little
- Quite a bit
- Very much

#### 2. Functional Assessment of Chronic Illness Therapy or Cancer Therapy (FACT)

The general questionnaires (FACT-G) consists of four domains (see below), there are also disease and treatment specific questionnaires e.g. FACT-O, ovarian cancer and FACT-D, diarrhea. See [www.facit.org/facitorg/overview](http://www.facit.org/facitorg/overview).

- Physical
- Social/Family
- Emotional
- Functional Well-Being

Answers are graded on a 5-point scale

- Not at all
- A little bit
- Somewhat
- Quite a bit
- Very much

## Section 2. National infrastructure for cancer care

### 2.1 Organisation of cancer services

The UK has an international reputation for cancer research and has a highly developed and effective infrastructure to enable the timely set-up and delivery of cancer research studies.

#### England

The National Institute of Health Research (NIHR) Clinical Research Network (CRN) facilitates participation in clinical research studies within the NHS. The CRN is made up of 15 Local Clinical Research Networks across England. The CRN manages the national and local delivery of research across 30 clinical specialties, including cancer. Each of the 15 Local CRNs has identified Cancer Subspecialty Champions consisting of around 200 research-active clinicians who work at both local and national levels to deliver cancer research studies.

The role of the CRN cancer specialty is to ensure that cancer studies included in the NIHR portfolio of studies receive the right support to ensure they are delivered successfully in the NHS. They work in close partnership with the National Cancer Research Institute (NCRI) and a wide range of stakeholders, including cancer research charities, the Experimental Cancer Medicine Centres (ECMCs) and clinical trials units to deliver a continual pipeline of high quality research studies which improve the diagnosis, treatment, care and outcomes of cancer patients. For more information on the CRN cancer specialty visit [www.nihr.ac.uk/cancer](http://www.nihr.ac.uk/cancer).

#### Northern Ireland (NI)

The Northern Ireland Cancer Network is a partnership of Health & Social Care Northern Ireland (HSCNI) organisations, academia, charity, cancer specialists and service users working in collaboration to deliver safe and effective care, improve cancer clinical outcomes and enhance patients and carers experience and quality of life.

The Network was formed in 2004 as NI's first Regional Clinical Network and links together the organisations that provide care for people with cancer across the 5 Health & Social care trusts in Northern Ireland. The Network is part of the Health and Social Care Board. The Network does not actively deliver patient care, but works closely with service users, health professionals and managers to improve cancer services and to implement national and local NHS strategies.

They:

- support their members in the delivery of services that are evidence based.
- ensure equity of access and uniform quality of services for the population of NI, and
- work across organisational boundaries following the patient pathway.

Adapted from [www.cancerni.net/](http://www.cancerni.net/).

#### Scotland

The Scottish Cancer Research Network (SCRN) is an initiative supported by the Chief Scientist Office (CSO) of the Scottish Government to increase, support and sustain clinical trial activity in cancer care in partnership with the UK Clinical Research Collaboration (UKCRC).

The SCRN aims to support recruitment of cancer patients into clinical research across Scotland. The network is divided into regions: the North, East, South East and West. Each region has a Clinical Lead and a Network Manager to support their regional trial portfolio and research teams. The clinical research supported by the SCRN is peer reviewed, quality research that is included in the NIHR clinical trial portfolio or considered eligible by the CSO in Scotland. For more information visit [www.nhsresearchscotland.org.uk/research-areas/cancer/about-the-network](http://www.nhsresearchscotland.org.uk/research-areas/cancer/about-the-network).

#### Wales

The Wales Cancer Network (WCN) was officially formed in October 2016, evolving from the merger of the two Cancer Networks in Wales and the Cancer National Specialist Advisory Group.

The WCN aims to deliver a new structure and approach to cancer in Wales seeking to not only simplify the organisational landscape of cancer services in Wales but to provide a single, patient focused, clinically led organisation integrating Welsh Government, Health Boards and cancer service stakeholder groups including

the 3rd sector; it provides the drive and source for intelligence, innovation and improvement and is formally linked into health board planning, performance and policy functions. Wales has its own single cancer pathway. For more information visit [www.walescanet.wales.nhs.uk/home](http://www.walescanet.wales.nhs.uk/home).

## 2.2 Experimental Cancer Medicine Centre (ECMC) Network

The ECMC Network is a joint initiative between CR UK and the UK Department of Health. The aim of the ECMC is to bring together laboratory and clinical patient-based research to speed up the development of new therapies and biomarkers by evaluating new drugs to optimise, target and individualise patient treatment. The ECMC Network is made of up 18 adult and 11 paediatric centres. The centres take ideas from laboratory programs and develop them into early phase clinical studies. For more information visit [www.ecmcnetwork.org.uk/](http://www.ecmcnetwork.org.uk/).

## 2.3 National Cancer Research Institute (NCRI)

The NCRI was set up in 2001, building on an informal collaboration between cancer research funders, with a mission to bring together the key opinion leaders in cancer research in the UK, to identify where research is most needed and where it is most likely to contribute to progress. The NCRI has several different strands of work to support coordination in UK cancer research including the Clinical Studies Groups, the Cancer CTU Group and CT-Rad, which are described in more detail below. For more information on the NCRI visit [www.ncri.org.uk/](http://www.ncri.org.uk/).

### NCRI Clinical Studies Groups

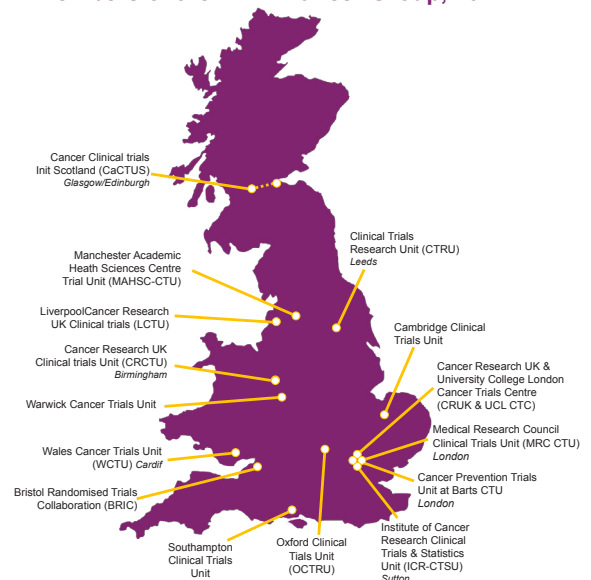
The Clinical Studies Groups (CSGs), sitting within the NCRI Clinical Research Groups Team, represent a central component of the framework for cancer research in the UK, providing the primary, but not sole, route through which new ideas for clinical trials are developed. There are approximately 20 NCRI CSGs, including cancer site-specific groups and cross-cutting groups. The CSGs are funded by a consortium of NCRI partners. The CSGs bring together clinicians, scientists, statisticians and lay representatives to coordinate development of a strategic portfolio of trials within their field. Some cancer research funders expect researchers to engage with the relevant CSG at the concept development stage. For more information visit <http://csg.ncri.org.uk/>.

### NCRI Cancer CTU Group

Clinical Trials Units (CTUs) play a pivotal role in delivering UK research, from the design and delivery of trials, to analysis and publication of results. NCRI Cancer CTUs have recognised competency in the design, delivery and analysis of cancer trials. NCRI Cancer CTUs often choose to specialise in a particular phase of trial or a particular disease area, and become hubs of academic expertise. There are currently 15 CTUs within the NCRI Cancer CTU Group. Membership of the group is based on the volume of multicentre, interventional cancer trial activity on the national portfolio. For more information visit [www.ncri.org.uk/accelerating-cancer-research/ctu/](http://www.ncri.org.uk/accelerating-cancer-research/ctu/).

The NCRI Cancer CTU Group Directors meet annually, there is an Operations Subgroup and a Training Subgroup. The NCRI Cancer CTU Group host an annual meeting.

Members of the NCRI Cancer Group, 2014



### NCRI Clinical and Translational Radiotherapy Research Working Group CTRad

CTRad is an NCRI working group set up in 2009 to develop a portfolio of practice-changing trials in radiotherapy and radiobiology, ensure coordination across research and actively promote translation of new discoveries into practice. A core part of CTRad's work is to support the development of radiotherapy research proposals through its Radiotherapy Clinical Trials Advisory Service (RADCAS) and through proposals guidance meetings providing pre-submission peer input to facilitate successful funding applications. For more information visit <https://ctrad.ncri.org.uk/>.

## Radiotherapy Trials Quality Assurance (RTTQA)

The RTTQA team was setup to ensure that patients in all NCRI radiotherapy trials adhere to a trial protocol, and are treated according to nationally accepted standards. This is an integral part of radiotherapy clinical trials and serves to minimise variations, ensuring clinical trial outcomes reflect differences in randomisation schedules rather than departures from the trial protocol. The team is closely linked with CTRad's Work stream 4 which leads on technical aspects of radiotherapy development. RTTQA designs and implements quality assurance programmes for all NIHR CRN Clinical Research Portfolio trials that include a radiotherapy component.

## 2.4 NIHR Chemotherapy and Pharmacy Advisory Service (CPAS)

The CPAS aims to help investigators manage risks associated with prescribing, preparing and administering chemotherapy. CPAS reviews protocols and associated documentation to ensure information regarding the management of study drug is appropriate and aims to achieve some consistency across the Network. CPAS has produced several guidance documents to advise investigators on the drug content and details of their protocols, and to assist the review process. For more information visit [www.nihr.ac.uk/nihr-in-your-area/cancer/cpas.htm](http://www.nihr.ac.uk/nihr-in-your-area/cancer/cpas.htm).

## 2.5 National cancer registries

The population level cancer registries in England, Northern Ireland, Scotland and Wales collect information about every patient diagnosed with cancer, including diagnoses (tumour type, stage and grade) and treatments. Cancer registries are allowed by law to collect this information to better understand and treat cancer. Access to this information is strictly controlled. The national registries are as follows:

- National Cancer Registry Ireland
- Northern Ireland Cancer Registry
- Public Health England
- Scottish Cancer Registry
- Welsh Cancer Intelligence and Surveillance Unit

## National Cancer Registration and Analysis Service (NCRAS)

NCRAS was formed by a merger of the National Cancer Intelligence Network and National Disease Registration. NCRAS aims to collect data on all cases of cancer that occur in people living in England. The data is used to support public health, healthcare and research. NCRAS provides data to the Office for National Statistics on new cases of cancer and cancer survival, monitors new cases of cancer in the population and looks at trends and geographical patterns in order to detect risk factors and cancer clusters. NCRAS operates a number of analytical partnerships, focussing on specific areas such as early diagnosis work with CR UK and survivorship with Macmillan. Data are shared between cancer registries and may be released to NHS organisations and healthcare professionals providing care for those patients; or monitoring the quality of cancer service provision. Data are also released for research uses. Data are normally released in an anonymised form so no individuals can be identified. Requests to access potentially or explicitly identifiable data are handled by the Public Health England Office for Data Release (PHE ODR).

## 2.6 Cancer charities

Cancer Research UK is the world's largest independent cancer research charity, and the single biggest charitable funder of cancer research in the UK. Their funding covers a wide range of activity, from basic research to late phase clinical trials. Cancer Research UK also provides core funding for a number of CTUs which have a specific focus on cancer clinical trials. For more information on Cancer Research UK funding schemes and application processes visit [www.cancerresearchuk.org/funding-for-researchers](http://www.cancerresearchuk.org/funding-for-researchers).

Many other UK charities fund cancer research with a focus in specific disease areas, including:

- Bloodwise
- Breast Cancer Now
- The Brain Tumour Charity
- Leukaemia and Lymphoma Research
- Myeloma UK



- Pancreatic Cancer Research Fund
- Prostate Cancer UK
- Roy Castle Lung Cancer Foundation
- Yorkshire Cancer Research

Further information about funding schemes and application processes can be found on the relevant charities' websites.

# Section 3. Regulatory framework

## 3.1 Trial design and regulatory considerations

### IMP definition

Many cancers are treated with multiple drugs. An important consideration is to determine which drugs are classed as an IMP and which are non-IMP's (NIMP's) within a trial. See MHRA website. [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/317952/Algothrim.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf). In addition, many cancer trials test drugs outside of their licensed indication, for example drugs licensed for common cancers are tested in rare cancers or drugs used for non-cancer diseases being tested for anti-cancer efficacy. Although the side effects may be well known, and manageable, within the licensed indication any use outside of this, would not be considered low risk from a regulatory perspective.

### Informed consent

Despite having a potentially life-threatening illness adults with cancer are not normally considered as a vulnerable population. The exception to this may be patients with primary or metastatic brain cancer. Their capacity to consent may need to be assessed and, to ensure patients are fully informed as their disease progresses, consideration may be given to obtain carers consent. Children with cancer should be informed according to current guidelines for paediatric patients.

### Biomarker driven trials

As many cancer trials are biologically driven with biomarkers defining eligibility or treatment choice, and often utilise novel techniques or designs, there is a need to consider the regulatory implications when developing trials of IMP's of this type. This may include:

- Considering whether a scientific advice meeting is required with the MHRA prior to submission of a Clinical Trial authorisation (CTA) to ensure that novel designs or endpoints satisfy regulatory expectations.
- Consideration of marketing status of assays used to assess biomarkers (in vitro diagnostics are considered to be medical devices).
- Considering the validity of biomarkers used to confirm eligibility or guide treatment choice.

A number of guidance documents are available from the MHRA and European Medicines Agency (EMA) regarding regulatory expectations for biomarker driven research including:

- MHRA Guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC
- EMA reflection papers for laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010)
- EMA guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)
- ICH Topic Q (r1) – 'Validation of analytical procedures' (CPMP/ICH/381/95)

**Inspection:** There is an increased regulatory inspection focus on laboratories that conduct biomarker analyses for clinical trials. Consideration should therefore be given to the governance arrangements in place for these laboratories. The UKCRC Registered CTU Group has developed guidance documentation around Good Clinical Practice expectations for laboratories. Further information is available at [www.ukcrc-ctu.org.uk/page/Guidance](http://www.ukcrc-ctu.org.uk/page/Guidance).

## Section 4. Trial planning and development

### 4.1 Expert opinion / pre-grant funding review

There are several national cancer specific groups to aid investigators and trial managers in the design and planning of trials. These include:

- **NCRI Clinical Studies Groups (CSGs)** <http://csg.ncri.org.uk/> - see Section 2.
- The opinion of the relevant NCRI CSG is essential for grant applications. The CSGs can give valuable advice and will know of any other trials planned that may compete for the same patients.
- **NIHR Chemotherapy and Pharmacy Advisory Service (CPAS)**  
[www.nihr.ac.uk/nihr-in-your-area/cancer/cpas.htm](http://www.nihr.ac.uk/nihr-in-your-area/cancer/cpas.htm) - see Section 2.  
CPAS aims to help trials to run as smoothly and quickly as possible and to improve quality of care and management of risks in prescribing, preparing and administering chemotherapy. The main areas which cause delays and problems and have made clinical trials difficult to implement include:
  - Dose adjustments
  - Dose capping
  - Missing pharmacy information
  - Supply of drugs
  - Safe administration of chemotherapy

CPAS aims to help investigators through any problems, achieving some consistency across the Network by reviewing clinical trial protocols and pharmacy related documentation.

- **British Oncology Pharmacy Association (BOPA)** [www.bopawebsite.org/](http://www.bopawebsite.org/).  
The purpose of BOPA is to promote excellence in the pharmaceutical care of patients with cancer through education, communication, research and innovation by an alliance of hospital, community and academic pharmacists, pharmacy technicians, those in the pharmaceutical industry and other healthcare professionals. They provide training opportunities and guidance information related to cancer clinical trials.
- **NCRI Clinical Trial Pathology Advisory Group (CTPAG)** <http://cmpath.ncri.org.uk/ct-pag/> This recently formed group sits within the NCRI initiative in cellular molecular pathology. Its membership includes pathologists, scientists, statisticians, bio-informaticians and consumer representatives. CTPAG aims to provide guidance and critique of pathology and biomarker components in clinical trials.
- **NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad)**  
<http://ctrad.ncri.org.uk/> - see Section 2.  
The CTRad is an NCRI working group set up in 2009 to develop a portfolio of practice-changing trials in radiotherapy and radiobiology, ensure coordination across research and actively promote translation of new discoveries into practice. The QA support team can also advise on the set-up of NIHR CRN Portfolio trials with a radiotherapy component.  
  
Support and guidance is available for trials involving radiotherapy and radiation/drug combinations. Proposal guidance meetings provide an opportunity for investigators to present a proposal for discussion and peer feedback, prior to making a funding submission. Some funders will expect that such input has been sought in advance of a funding application.

### 4.2 Funding and peer review

There are several organisations within the UK that fund cancer research. In addition to the NIHR and MRC there are several charity organisations within the UK that provide funding for cancer research e.g. CR UK. These are listed in the AMRC member's directory. Each have their own particular funding calls and peer review systems, see [www.amrc.org.uk/Pages/Category/member-directory](http://www.amrc.org.uk/Pages/Category/member-directory).

### 4.3 Protocol development

#### Defining chemotherapy agents that are Standard of Care (SOC) or IMP:

It is important that the protocol clearly defines which drugs are IMPs and which are classed as NIMPs. Many cancer trial protocols involve the delivery of complex chemotherapy regimens, not all of which are the focus of the research question, but are instead standard care therapy which must also be delivered to ensure appropriate treatment of the cancer (i.e. 'background' therapy). In assessing which drugs should be designated as IMPs it is important to identify which drugs are the focus of the research to answer the research questions the trial is designed to answer (i.e. the trial objectives). Careful consideration should be given as to whether established therapies given as standard care in the trial population may be classed NIMP, considering the objectives of the study.

Drugs designated as IMPs must fulfil stringent manufacturing criteria as required by the EU Clinical Trials Directive (2001/20/EC) which may require the input of a Qualified Person (QP) and QP certification of the product.

For every drug classified as an IMP, pharmacy need to provide resource and suitable facilities for IMP receipt, temperature monitoring, storage, preparation, dispensing, labelling, accountability, monitoring, code breaking, return and/or destruction. See 4.5 for further details to assist with costings.

Thus, the inappropriate classification of drugs as IMPs may result in hospital pharmacy services being unable to support the study due to the excessive amount of resource required for dealing with all the IMPs. This may be addressed by the sponsors careful consideration of the classification of drugs used in the protocol before submitting the IRAS form and requesting regulatory approval (MHRA Clinical Trial Authorisation).

Guidance on the designation of IMPs in clinical trials can be found in the EU Clinical Trials directive [2001/20/EC], article 2 (d), and the European Commission document: Eudralex Volume 10 (Clinical Trials) Chapter V – Additional Information – 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials'.

### 4.4 Defining standard of care - interventions and tests

Other interventions, treatments and tests that should be considered when developing the protocol as standard of care or research procedures include:

- Surgical Procedures
- Radiotherapy
- PET scans
- MRI scans
- Sample collections – pathology, blood samples, tissue

### 4.5 IMP management

This is an extremely important area that needs to be considered and costed appropriately at the development stage of any cancer clinical trial that involves an IMP. Therefore, early communication with the pharmaceutical company or third-party vendor is extremely important at this stage to ensure IMP is available at site for the clinical trial. Considerations include the following:

- **CPAS:** Submitting the study protocol to CPAS for review. CPAS have a Protocol Template Guideline and Cancer Pharmacy Manual for cancer chemotherapy clinical trials.
- **Oral medication:** To consider whether the patients are able to swallow the oral drugs and whether the drugs need to be consumed with food, certain drinks, on an empty stomach.
- **Patient drug diaries:** This may be necessary if patients are taking any medication at home.
- **Defining the IMP:** To use the generic drug or specific brand.
- **IMP availability:** Will a company be providing the drugs or will it have to be procured through a central pharmacy or company? Will appropriate licences be required e.g. for import?
- **Manufacturing lead times:** e.g. in early phase trials where manufacturing runs, batches may be small.

- **Blinded Study:** does the study require a placebo? Will this be provided by the company? Does the placebo need to be manufactured?
- **Shipping of Drugs into the UK:** To consider how this will be managed, costed adequately.
- **Distribution of IMP** and patient IMP kits to sites.
- **Packaging and Labelling.**
- **QP release.**
- **Long term supply arrangements:** Will the drug be available to patients at the end of the study if the patient is benefiting from the treatment.
- **Toxicities.**
  - British National Formulary [www.bnf.org/bnf](http://www.bnf.org/bnf).
  - Summary of product characteristics and patient information leaflets for all UK licensed drugs [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc).
- **Costs** – Is the IMP or placebo VAT exempt if being procured for the study? Shipping Fees needs to be considered if the IMP or placebo is being procured from abroad?
- **Storage requirements.**
- **Drug stability & expiry dates.**

#### 4.6 Patient and public involvement (PPI)

- **NCRI consumer clinical studies group and liaison** <http://csg.ncri.org.uk/>.  
NCRI CSG consumers are members of the NCRI Consumer Forum. The forum aims to foster a vibrant and collaborative community to work with NCRI as partners in cancer research; exchanging knowledge and expertise in a coordinated way.
- All NCRI's clinical research activities have consumer members (patient/carer representatives), such as on the 20 NCRI Clinical Studies Groups (CSGs). Consumer members participate in all aspects of the CSGs activities.

This group can also support identification of PPI representatives for review of trial documents such as information sheets, consent forms and adverts, if you don't have a mechanism locally.

- **Independent Cancer Patient Voices (ICPV)**  
ICPV is a patient advocate group independent of established UK cancer charities and aware of the value of medical research to both public health and to the national economy. Their aim is to improve existing treatments for every cancer patient and develop new treatments by bringing the patients' voice into clinical research. Members are involved in the design and running of a number of clinical studies, helping to ensure that they are targeted effectively. They work as advocates at a strategic level with clinicians and clinical researchers in order to improve clinical research and outcomes for all cancer patients.

#### 4.7 Long term follow-up & options/requirements for obtaining outcome data

Participants involved in cancer trials may be followed up for long time periods (10 years+), particularly where overall survival is an outcome measure, and long term follow-up data may be obtained from a variety of sources. Requests for long term follow up data may be made periodically to participating sites using Case Report Forms (CRFs). Death certificates may be collected alongside CRF data. This requires resource and engagement at local sites and can be problematic.

To collect these data, participating sites may use telephone follow-up for participants who have been discharged from clinical review. Follow-up by email may be permitted subject to local Information Governance policies. Patient-reported outcomes may also be collected where this is considered to be feasible.

Where data collection via CRF is not possible, information may be obtained from Hospital Episode Statistics in conjunction with NCRAS (see section 2.5). NCRAS collects data on all cancer cases in England to support research. Relevant data may be available for research purposes and requests to access data are handled by the Public Health England Office for Data Release (PHE ODR). Formal requests for release of data can be made and will only be approved for release where the data is being used for a medical purpose.



It is imperative that the follow-up schedule is clearly defined in the protocol. The Patient Information Sheet must clearly state follow-up details to ensure that participants are aware of how data will be collected, the duration of data collection, how the data will be stored, who will have access and the retention period. Any changes to this must be subject to ethical review and may require re-consenting.

### Online cancer trial databases

Cancer Trial Databases are an excellent source of information for researchers to stay up to date on developments in a particular field, to find potential collaborators, and identify groups of cancer patients with unmet needs:

- EORTC database of EORTC clinical trials [www.eortc.org/](http://www.eortc.org/).
- National Cancer Institute US - database of clinical trials [www.cancer.gov/](http://www.cancer.gov/).
- UKCRC Gateway / NIHR Trials portfolio database - database of all UK academic cancer trials [www.ukctg.nihr.ac.uk/](http://www.ukctg.nihr.ac.uk/).

### 4.8 Site feasibility questionnaires

Some cancer clinical trials can include complicated treatments, interventions, investigations and sample collection and processing. To identify potential recruitment centres for a study it is advisable to send out a site feasibility questionnaire to sites to see if they have the capacity and capability to deliver the requirements of the trial i.e. PET-CT scans, novel delivery systems for cancer chemotherapy/immunotherapy treatments, Pharmacy support (storage, staffing, timelines for time sensitive preparations), specialist radiotherapy, surgery, laboratories and equipment for processing and storing clinical trial patient samples etc. In many cancer trials different aspects of the protocol procedures can be delivered at more than one site i.e. "shared care" and this can differ across the UK.

This can also be used to understand how many potential patients are seen by the clinical teams at the sites which may be suitable for the trial. This information will help to design the study and determine the recruitment period with the number patients from the potential sites.

### 4.9 Quality assurance

Quality Assurance is essential to ensure clinical trials are conducted to UK and international regulatory requirements, Good Clinical Practice (GCP) and ethical and scientific quality standard for designing, conducting, recording and reporting trials. Quality Assurance is maintained and monitored through a Quality Management System (QMS) which provides a framework to ensure quality in all clinical study activities and that they are conducted in accordance with approved study documentation.

Quality Management System may consist of:

- Standard Operating Procedures (SOPs) for all clinical trial activities which are continuously, reviewed and updated as required.
- Document Management System to ensure all SOPs and approved documentation for a clinical trial are stored and version-controlled and to be able to retrieve any records or documentation during the life cycle of a trial to show actions taken, decisions made and results.
- Quality Manual which defines the organisational structure and accountability with defined roles and responsibilities.
- Appropriate documented training of staff depending upon their responsibilities on the trial and GCP training.
- Validated computerised systems.
- Quality Control (QC) activities: monitoring of trial sites either on-site or through centralised or remote monitoring procedures.
- Quality Assurance (QA): Audits of QMS systems and processes and individual clinical trials.
- Risk Assessments.
- Continuous improvement incorporating Corrective and Preventive Actions (CAPA).

QMSs should also be in place for the collection and analysis of samples at sites and laboratories. This is detailed in section 4.10.

## 4.10 Sample collection, processing, storage and shipment

For clinical trial with a sample collection component, it is recommended to work with a laboratory that works to GCP standards and have all the relevant the quality systems in place to ensure sample and data integrity.

The analysis of biological samples collected from subjects participating in cancer clinical trials forms a key part of the clinical trials process and provides important data on a range of endpoints, eligibility and stratification. Typical laboratory analysis for a clinical trial could include pharmacokinetic or pharmacodynamic profiling of an IMP, monitoring safety, tolerability and efficacy as well as identifying biomarkers. It is therefore essential that sample, collection, processing and analysis or evaluation is performed to a high standard at both clinical trial sites and the laboratory to ensure that patient safety is not compromised and that data is auditable, reliable and accurately reported.

Relevant regulatory and ethical approvals must be in place to allow for the collection of samples from clinical trial subjects, for example specific consent must be obtained to analyse genetic material and consideration should be given to when happens to the samples at the end of the trial.

During the development of a clinical study, especially when the primary and/or secondary endpoints are laboratory based, careful consideration must be taken to select the relevant samples, method of collection and processing that will be needed in order to answer the research questions. For primary and secondary endpoint analysis, there should be a minimum level of validation carried out to ensure that the collection and processing methods are suitable for the required analysis, for example, the maximum time from blood collection to processing should be defined along with the type of blood tubes to be used (e.g. EDTA, Lithium Heparin, Serum).

Consideration must be given to:

- the appropriate biological samples to be collected.
- the collection time points (when during the study schedule should samples be collected and which samples).
- the method of sample collection, processing and storage must be defined in a translational protocol or laboratory manual which is supplied to sites.
- long-term or temporary storage at clinical trial sites.
- transfer of samples from clinical trial sites and the conditions needed, for example ambient, dry ice or liquid nitrogen.
- monitoring of sample transfer should be risk assessed, primary or secondary endpoint samples transferred at low temperatures should be temperature monitored.
- monitoring of samples through appropriate sample tracking and laboratory information management systems.
- a quality management system and appropriate SOPs.
- ensuring adherence at all times to regulatory requirements related to sample collection.

In all cases it is important to consider the costs of sample collection for studies, in particular the costs for assay validations, sample collection kits, transport of samples from sites to the laboratories, temperature logging during transit, sample analysis, sample storage, in particular long term storage at low temperatures, equipment costs, environmental monitoring systems , quality systems and staff time.

### Types of Samples

Many different types of samples may be collected for a clinical study depending on the primary/secondary outcome and research objectives. This could be:

- blood and blood fractions (plasma, serum, buffy coat).
- tissue samples (fresh frozen, formalin fixed paraffin embedded, preservative).
- faecal samples.
- urine.
- saliva/buccal cells.
- bone marrow.
- fluids from Cytology.

## Types of Sample Collections

The sample collection procedure will be dependent upon the type of sample to be collected, as previously mentioned the collection and processing procedure should have been validated, especially for primary/secondary laboratory endpoint.

Detailed guidelines on this can be found in the following publication:

Molecular Epidemiology: Principles and Practices, International Agency for Research on Cancer Scientific Publication No 163, Unit 2, Chapter 3, page 27 – 30. <http://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Molecular-Epidemiology-Principles-And-Practices-2011>.

## Sample Collection Kits

It is recommended that sample collection kits, containing everything needed for the sample collection, are used per time point per patient. The kits are provided to sites at initiation and throughout the study as needed. This therefore needs to be considered at the early stages of developing a clinical trial to ensure the correct kit components, sample tracking, quality systems and processes are considered. This should be developed with the laboratories that will be supporting the sample collection protocol.

The following should therefore be considered when developing sample collection kits for a clinical study, but is not an exhaustive list:

- Sample collection tubes or pots required for all patients at each study time point (such as EDTA blood tubes, Lithium Heparin blood tubes, serum separator blood tubes, faecal collection pots, urine pots, microbiome swabs, saliva swabs etc.)
- Laboratory Information Sheets to inform the laboratory of relevant information about the sample.
- Sample tracking forms to inform the CTU about the sample so it can be linked to a patient and time point.
- Biological sample postage pouches and boxes (e.g. Pathosheild).
- Unique Labels on all kit components to allow for the sample to be linked to the patient and time point whilst maintaining blinding of the laboratory.
- Suitable courier for shipment of samples – able to transport samples to study requirements to ensure the integrity of the sample and able to provide adequate sample tracking information. Do samples need to be shipped on dry ice?

It is important that site staff responsible for collecting samples are adequately trained during the initiation of a study before they are able to ensure samples will be collected correctly for all patients in the study. They should also be provided with a laboratory manual to instruct them on the sample processing workflow and other key information. It is also worth considering video tutorials for complex sample processing or site visits by laboratory staff.

## Processing of Samples

Samples are processed according to the validated study requirements and are usually provided to sites in the form of a laboratory manual. Laboratory manuals must be written to fit the validated requirements for the biomarker/s to be investigated, for example maximum time between blood collection and processing, therefore ensuring the integrity of the sample at all times. This must be considered at the development stage of a study. Processing of samples may occur at site and/or within the research laboratories. The processing of samples must be accurately documented within a laboratory manual (sites) or SOPs (laboratory) before a study commences to recruitment.

Processing of samples include:

- **Blood:** separation by centrifugation into fractions such as plasma, buffy coat, serum, red blood cells. Methods include cryopreservation.
- **Tissue:** processing after surgery or autopsy. May be processed soon after in theatre or in the pathology laboratories.
- **Urine:** aliquoted into smaller tubes for storage.
- **Saliva/buccal cell processing from mouthwash** protocol specimens. Collected by centrifugation of the cell suspension with a buffer.
- **DNA Extraction:** From blood samples, urine, buccal cells, fresh and frozen tissue and paraffin tissue blocks.

## Storage of Samples

It is critical to maintain careful records of the identity and location of all materials whether at sites or in the laboratory, with particular attention to storage history, occurrence of temperature fluctuation and monitoring of stored control specimen in order to check the effects of storage duration. Specimens and aliquots of samples may be stored under a variety of conditions. Laboratory manuals, SOPs and work instructions must be in place for the storage of samples and what to do in case of any emergencies such as system failures and transfer of samples to back up facilities.

General storage conditions to consider:

- Adequate storage facilities, at the correct temperature are in place for all samples collected during a study with enough capacity and resources for the lifetime of the study, any follow up period and archiving.
- Back up facilities and equipment in place.
- Power supplies to equipment are connected to back up generators.
- For samples being stored in liquid nitrogen, ensuring adequate supplies and monitoring is maintained at all times.
- All freezers and liquid nitrogen tanks should be fitted with environmental monitoring systems and alarms to inform of any temperature deviations and alert staff of any equipment failures.
- Systems validations have been completed.
- Servicing of equipment.

## Laboratories working to Good Clinical Practice Standards

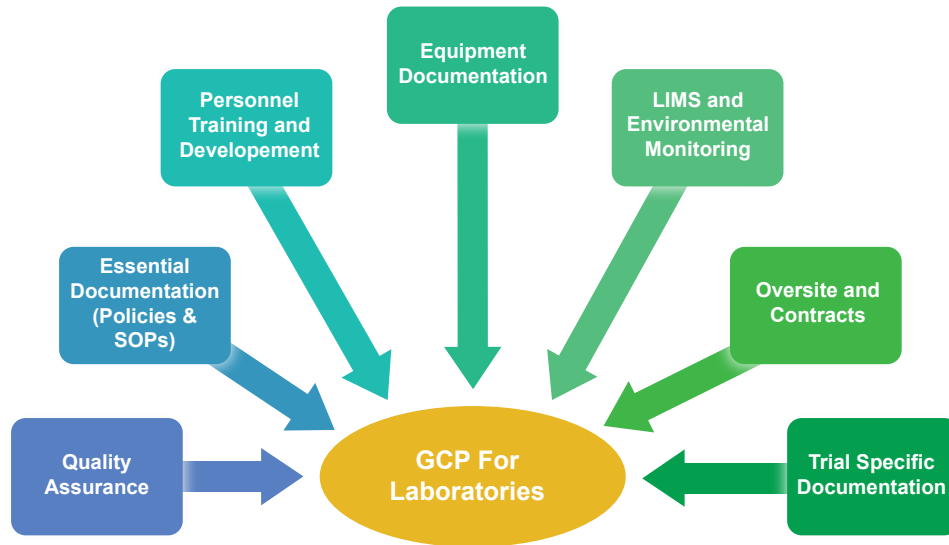
Some clinical trials have laboratory-based analytical (primary or secondary) end-points defined in the clinical trial protocol. The MHRA expects all laboratory samples analyses to be carried out to Good Clinical Practice standards in the central laboratory so that the data produced are auditable, reliable and fully documented. This is critical to the outcome of the trial and used to guide future development or subsequent trials. This therefore should be considered when setting up a clinical trial and working with a laboratory that works to GCP to determine the requirements for sample collection, processing and analysis.

How do laboratories work to GCP?

- The laboratories should have a robust QMS, secure security and IS systems, document management, computerised inventory, specimen quality tracking systems and disaster recovery plan.
- All work is carried out using SOPs produced before any work can begin.
- Roles and responsibilities within a laboratory should be established and documented prior to the initiation of analytical work. Laboratory staff undergo regular training in GCP. Training also applies to the equipment used in the laboratories.
- Equipment is quality controlled on installation (Installation Qualification- IQ) and only used for the purpose specified. This requires independent Operational Qualification (OQ) certification and Performance Qualification (PQ) control.
- Records of the quality control and maintenance of equipment are stored and can be cross-referenced with laboratory books or Laboratory Information Management Systems (LIMS).
- Data integrity is best demonstrated by a robust, auditable, reliable and reproducible processing and analytical method that is validated. Method should be validated prior to undertaking sample collection and analysis.
- Any experiment undertaken in the laboratories can be inspected with the confidence that a commitment to use a given protocol was made before the experimental data were obtained and that all of the data were stored including any negative experiments.
- Essential that work carried out is stipulated in the necessary contracts, clinical trial protocol and relevant work instructions. Contracts should identify the standards to which the work should be conducted (including relevant regulations and guidelines). There must be consistency between these documents and this should be verified by the sponsor and laboratories. Sponsor's responsibility to ensure that version of the protocol (or part thereof) provided is current and has not been subject to amendments. A mechanism should be agreed with the sponsor to ensure relevant amendments to the clinical protocol are supplied to the laboratories accordingly and in a timely fashion. Laboratory

requirements include constant monitoring of all storage conditions and meticulous longitudinal recording of all environmental changes that might affect each and every sample.

### GCP requirements for Laboratories



### References for Regulations and Legislation related to GCP Laboratories:

- Good Clinical Laboratory Practice, ISBN 1-904610-00-5, 2003.
- RQA -Good Clinical Laboratory Practice: GCLP a Quality System for Laboratories that undertake the Analyses of Samples from Clinical Trials.
- EMA: Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples February 2012. [www.ecmcnetwork.org.uk/sites/default/files/EMAReflectionPaper\\_PStewart.pdf](http://www.ecmcnetwork.org.uk/sites/default/files/EMAReflectionPaper_PStewart.pdf).
- England and Wales Human Tissue Act 2004, Scotland Human Tissue Act 2006.
- Molecular Epidemiology: Principles and Practices, International Agency for Research on Cancer Scientific Publication No 163, Unit 2, Chapter 3, page 27 – 42. <http://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Molecular-Epidemiology-Principles-And-Practices-2011>.



## Section 5. Trial set up

As for all trials, the set-up phase for a cancer clinical trial is particularly important and there are a number of factors specific to cancer patients that need to be considered when setting up a trial in the cancer setting. For example the patient care pathway, referral processes, treatment centres/hospitals, patient follow-up, cancer waiting times and availability of interventions such as Radiotherapy, PET-CT, Nuclear Medicine and surgical specialities. There will be some overlap with the planning and development of a clinical trial.

### 5.1 Cancer patient waiting times

The National Institute for Health and Care Excellence (NICE) have referral guidelines in place for any suspected cancers. The identification of people with possible cancer usually happens in primary care, as the large majority of people first present to a primary care clinician. The guidelines cover the recognition and selection for referral or investigation in primary care for children, young people and adults who may have suspected cancer. The guidelines are also to help those in secondary care to understand which services should be provided for people with suspected cancer.

These recommendations are not requirements and are not intended to override clinical judgement. In most cases patients are seen within the national target for cancer referrals - Suspected Cancer Pathway Referral.

Set targets have also been put in place for maximum waiting times from the time of receiving the urgent referral to start of treatment. The set waiting times are the same in England and Wales as well as those set by the Scottish Government and the Department of Health in Northern Ireland:

- No more than 2 months (62 days) wait between the date the hospital receives an urgent referral for suspected cancer and the start of treatment.
- No more than 31 days wait between the initial meeting with the clinician to agree the treatment plan and the start of treatment.

These guidelines are a useful information resource and the government set targets should be considered when setting up and designing a trial to understand:

- the referral process for a patient with a particular cancer.
- the initial investigations and interventions that are carried out to diagnose a patient with cancer.
- the standard patient pathway once a patient is diagnosed and the timelines for starting treatment.
- patient follow up and aftercare.

### 5.2 Consideration of participating sites

This is detailed in section 4. It is important to know if potential sites have the capability to deliver the trial and a trained research team.

#### Participating site study team

For cancer clinical trials it is important to consider the research team at site and who is required to complete the tasks listed on the delegation log. To ensure the successful delivery of the trial, engagement from all the relevant disciplines are required. This could include:

- Medical Oncologist.
- Clinical Oncologist.
- Surgeon.
- Oncology Research Nurse.
- Site Data Manager, Trial Practitioner etc.
- Pharmacist.
- Radiologists for reporting on CT scans, RECIST.
- Pathologists.
- Nuclear Medicine team.
- Laboratory staff – clinical laboratories and GCLP Labs.

### 5.3 Availability of study interventions and treatments

As some study interventions and treatments are specialised, they may be carried out at other sites, in which case consideration of governance and contractual arrangements may be required:

- Radiotherapy.
- PET-CT.
- MRI.
- Nuclear Medicine.
- Surgical specialities.
- Clinical Laboratory Tests.

### 5.4 Data collection issues that need to be considered in cancer trials

- **Radiotherapy QA**

Radiotherapy may be delivered and reported slightly differently in each study site. Consideration should be given to the quality assurance (QA) processes which will be implemented to ensure consistency e.g. for radiotherapy planning. RTTQA is a centralised resource providing a national RT trial QA programme for all NIHR CRN Clinical Research Portfolio trials that include a radiotherapy component [www.rtrialsqa.org.uk/rttqa/](http://www.rtrialsqa.org.uk/rttqa/).

Similar approaches may be necessary when it is important to ensure consistency of planning, delivery and reporting in other modalities such as surgery or imaging.

## Section 6. During the trial

### 6.1 Data collection and follow-up

With long term outcomes and overall survival being key efficacy endpoints for most cancer trials, consideration needs to be given to appropriate mechanisms for acquiring reliable long term follow up data whilst minimising the burden on patients, participating sites, CTUs and funders. Various methods can be employed including use of telephone follow-up, use of patient reported outcomes and use of national routine datasets (e.g. cancer registry data). The amount and type of data to be collected requires careful consideration as do the governance and regulatory implications of using alternative follow up methods. Collection of data from routine datasets is dependent on the type of consent obtained so appropriate wording in the consent form is key, as is the collection of specific identifiers (e.g. NHS/CHI number and postcode) to allow for data linkage. Also see section 4.7.

# Section 7. End of trial

End of trial issues that impact on cancer trials include the following:

## 7.1 End of trial definition

Defining the end of trial for cancer trials can be difficult, particularly where overall survival is an efficacy endpoint as follow up may continue indefinitely. For this reason, end of trial is often defined as date of last data capture.

## 7.2 Treatment beyond the end of trial

For earlier phase cancer trials where progression free survival may be the key endpoint, consideration needs to be given to the time point at which no further data will be collected if, for example, one or two patients continue to do well on treatment after the protocol defined endpoint has been achieved. In these circumstances arrangements may need to be put in place to ensure patients can remain on treatment beyond the end of trial, for example via compassionate use programmes. The contract with any drug provider should make provision for this where possible.

## 7.3 Trial samples beyond the end of trial

The regulatory procedures for reporting the end of trial are standard across all disease types. However, specific consideration needs to be given to biomarker rich cancer trials in terms of tissue governance beyond the end of trial. Once the end of trial has been declared to the Research Ethics Committee (REC), the legal basis for holding the samples may no longer apply. Research tissue held outside of a current REC approval must be within a suitably licensed HTA facility or a REC approved biobank. After declaring the end of trial, consideration must be given to appropriate governance of remaining trial samples.

## Section 8. Preparation of final reports and publication

### 8.1 Disseminating information to cancer patients

Since survival is often an endpoint in cancer trials, and the obvious sensitivities concerning mortality, it is considered best practice to provide written results in lay terms to the clinicians responsible for the care of trial participants. Clinical teams should be asked to use professional judgement to decide when and how to convey results to individual participants and/or their next of kin.

Lay summaries should convey the results of the study in plain English and in a language that non-scientific readers can understand. Translation of results into a more accessible format (for example, use of “this means 1 in 1000 people” rather than percentages (absolute and relative risk)) is important, as is the involvement of a statistician to ensure that important statistical messages are not lost in any translation and the lay summary is factually correct. PPI input is also critical to ensure that the summary is understandable and any sensitive subjects are addressed appropriately, particularly where information about mortality is being conveyed. CR UK provides lay summaries of results for trials they have funded or endorsed.

For trials in cancers with relatively good prognosis, where disease free or overall survival endpoints may be expected many years after patients were recruited into the trial, it is considered good practice to inform patients of trial progress, for example notifying them when recruitment has completed or other major milestones have been achieved. Again, this should be done via the clinical teams responsible for the care of trial participants who are best placed to decide how to convey this information to participants and/or their next of kin.



# Section 9. Archiving

## 9.1 Provisions for data and tissue sharing beyond the trial

The availability of patient data and tissue collections is vital for research into cancer. Tissue and data collected within clinical trials are of a high quality – they are collected prospectively in a systematic and unbiased fashion and are well curated and documented. Trialists have a duty to facilitate responsible sharing of these collections with the wider research community. Sharing has the potential to improve scientific and medical knowledge, improve and validate research methods, encourage collaboration and reduce duplication of effort.

Sharing must take into consideration:

- the scientific integrity of the original trial and the proposed research.
- the terms of the consent with which tissue and data were collected.
- relevant governance and regulatory requirements.
- the terms and conditions of the sponsors and funders of the original trial.

Data and tissue sharing policies and formal access and approval processes are required to ensure that legal, ethical and commercial constraints are recognised and that collections are made available for new research in a responsible manner.

Data and tissue access policies should define:

- Governance arrangements
- Prioritisation criteria
- Eligibility requirements
- Limitations of access
- Conditions of access
- Access process

Trialists have a duty to ensure that the wider research community is aware of the data and tissue collections they hold. This can be achieved by declaration on institutional websites or registration of collections on national databases (e.g. UKCRC Tissue Directory).

Consideration should to be given to the physical location of data and tissue collections (i.e. electronic data archive, tissue held within an approved biobank), the governance arrangements and resource requirements to maintain collections beyond the end of the trial and facilitate sharing.

## Appendix 1. Useful acronyms

Acronym	Explanation
AE	Adverse Event
ATIMP	Advanced Therapeutic Investigational Medicinal Product
BOPA	British Oncology Pharmacy Association
CAPA	Corrective and Preventive Actions
CHI	Community Health Index number: unique patient identifier used in Scotland
CPAS	Chemotherapy & Pharmacy Advisory Service
CR	Complete Response
CRF	Case Report Form
CRM	Continuous Re-assessment Method
CRN	Clinical Research Network
CR UK	Cancer Research UK
CSG	Clinical Studies Group
CSO	Chief Scientist Office - in Scotland
CSS	Cause Specific Survival
CTRad	Clinical & Translational Radiotherapy Research Working Group
CT	Computerised Tomography Scan
CTU	Clinical Trials Unit
DFS	Disease Free Survival
DLT	Dose limiting toxicity
ECMC	Experimental Cancer Medicine Centres
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediamine Tetra-acetic Acid
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FACT	Functional Assessment of Chronic Illness Therapy or Cancer Therapy
GCLP	Good Clinical Laboratory Practice
HSCNI	Health & Social Care Northern Ireland
HTA	Human Tissue Authority
ICH	International Conference on Harmonisation
ICPV	Independent Cancer Patient Voices
IMP	Investigational Medicinal Product
IPS	International Prognostic Index
IQ	Installation Quality
iRECIST	Immunotherapy Response Evaluation Criteria in Solid Tumours
MAMS	Multi-arm Multi-stage
MDT	Multidisciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	US National Cancer Institute
NCRAS	National Cancer Registration and Analysis Service
NCRI	National Cancer Research Institute

Acronym	Explanation
NCI CTC AE	National Cancer Institute Common Terminology Criteria for Adverse Events
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NIMP	Non-Investigational Medicinal Product
OQ	Operational Quality
OS	Overall Survival
PD	Progressive Disease
PERCIST	PET Response Criteria
PET	Positron Emission Tomography
PFS	Progression Free Survival
PHE ODR	Public Health England Office for Data Release
PPI	Patient and Public Involvement
PQ	Performance Quality
PR	Partial Response
RQA	Research Quality Association
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QMS	Quality Management System
QP	Qualified Person
RADCAS	Radiotherapy Clinical Trials Advisory Service
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RTTQA	Radiotherapy Trials Quality Assurance
SAE/R	Serious Adverse Event/Reaction
SCRN	Scottish Cancer Research Network
SD	Stable Disease
SOC	Standard of Care
TNM	Tumour Node Metastases System of Staging
UKCRC	UK Clinical Research Collaboration
US	Ultrasound
WCN	Wales Cancer Network

# Appendix 2. Specialists involved in cancer patient care

## Multi-Disciplinary Teams

- NHS guidelines emphasise that people with cancer should be under the care of a multidisciplinary team (MDT). This is a team of health professionals who work together to decide on the best way forward for each patient. The MDT includes cancer specialists relevant to a particular tumour type e.g. prostate cancer, and other specialists such as palliative care physicians etc. They usually meet weekly to discuss patients' diagnosis and decide upon treatment plans. Patients potentially suitable for clinical trials are often identified during these meetings.

## Who does what?

### Clinicians – Consultants are Fellows of a Royal College (FRC)

- Haematologists: FRCP (Pathologists). They may prescribe chemotherapy and targeted agents.
- Medical Oncologist: FRCP (Physicians). They prescribe chemotherapy, hormonal and targeted agents.
- Clinical Oncologists: FRCR (Radiologists). Specialises in treating cancer with radiotherapy and can prescribe chemotherapy / hormonal and targeted agents.
- Surgeons: FRCS (Surgeons) Specialise in different types of cancer e.g. colorectal, breast etc. Apart from operating on patients they may prescribe some hormonal therapies. Plastic surgeons may be involved if reconstruction is required of an area where a cancer has been removed.
- Radiologists: FRCR (Radiologists). Specialise in imaging CT, MRI, PET etc. and may also deliver treatment under imaging e.g. radiofrequency, embolization etc.
- Pathologists: FRCP (Pathologists). Specialise in detecting cancer cells in tissue and cell samples.
- Other "ologists": There are a variety of doctors who specialise in specific areas of the body e.g. gastroenterologists who are involved in endoscopy of the colon and bowel. They may be involved in inserting stents to open important vessels or conducting biopsies or delivering treatment under imaging.
- Palliative care physicians: Specialise in symptom control throughout treatment and end of life care.

### Cancer Nurses

- Clinical Nurse Specialists: Is an expert nurse and consistent point of contact for the patient and their family offering knowledge and support throughout diagnosis, treatment and follow-up and working closely with other members of the MDT. These nurses specialise in specific tumour types and may help organise care between doctors and the other health professionals.
- Research Nurses: Are a key point of contact and co-ordinates the care of a patient whilst on a trial, this includes organising investigations and taking blood samples and, in some cases, giving the treatment, as well as offering knowledge and support to the patient and their family. They may also provide information to patients about clinical trials.
- Cancer Chemotherapy Nurses: These nurses arrange for and deliver chemotherapy and targeted agents to patients as part of routine care. They may also be involved with trial patients, the research nurses liaise closely with them and provide the relevant information to ensure that treatment is given according to the protocol.
- Cancer Research UK & Macmillan Nurses: Charities employ nurses on their telephone and online helplines who answer queries and provide advice on treatment and support services.

### Other Cancer Health Professionals

- Radiographers: Involved in radiotherapy planning and treatment
- The Clinical Trial Practitioner: Performs much the same role as the research nurse but will delegate certain clinical tasks to other members of the team. They are not nurses and usually come from a science background.

## Appendix 3. Staging systems

Cancers have been classified into different groupings since 1952 when the first staging system was developed. Thirty years later, a uniform approach to use the TNM system for all solid tumours was agreed. Staging allows groupings of patients according to their survival rates and using a standard system allows for proper comparisons to be made. Tumours may be confined to the organ of origin, the local /regional areas or may have spread to other parts of the body.

Accurately recording information on the extent of disease at is useful to; decide on appropriate treatment, indicate prognosis and evaluate the response to treatment.

**Solid tumours:** use the TNM staging system, last updated Dec 2017, 8th edition.

T is the extent of the primary tumour:

- X – primary cannot be assessed
- 0 – no evidence of primary tumour
- is – carcinoma in situ
- 1, 2, 3, 4 – increasing size and/or local extent of tumour

N is the absence or presence and extent of regional lymph node metastasis:

- X –regional lymph nodes cannot be assessed
- 0 –no evidence of lymph node metastasis
- 1, 2, 3 – increasing involvement of regional lymph nodes

M is the presence or absence of distant metastasis:

- X – distant metastasis cannot be assessed
- 0 – no evidence of distant metastasis
- 1, 2, 3, 4 – distant metastasis

**The clinical classification** (cTNM) is based on evidence before treatment, physical examination, imaging, endoscopy, biopsy etc. The pathological classification (pTNM) is based on the evidence obtained for pathological examination of the surgical specimen and, if removed, the regional lymph nodes.

Histopathological grading is also important to determine prognosis.

- GX – Grade of differentiation cannot be assessed
- G1 – Well differentiated
- G2 – Moderately differentiated
- G3 – Poorly differentiated
- G4 – Undifferentiated

Once a TNM has been assigned the categories are grouped into stages. E.g. T1, T2, N0 = Stage 1.

AJCC Cancer Staging Manual. Editors: Amin et al. (Eds.) 2017.

### Haematological tumours:

**Lymphomas:** Use the Ann-Arbor Staging system and separate prognostic scores depending on the type of lymphoma or leukaemia e.g. for B cell lymphomas (see below), follicular, Hodgkin, mantle cell etc.

- Ann-Arbor criteria: used for all lymphomas, a 5-point scale, as follows:

Stage 1. 1 lymph node and the surrounding area – often asymptomatic

Stage 2. 2 lymph nodes, both on same side of the diaphragm

Stage 3. cancer has spread to both sides of the diaphragm

Stage 4. diffuse or disseminated involvement of one or more extra-lymphatic organs

Hodgkin's Disease. Mauch, Peter; James Armitage; Volker Diehl; Richard Hoppe; Laurence Weiss (1999). Lippincott Williams & Wilkins. pp. 223–228. ISBN 0-7817-1502-4.



- International Prognostic Index (IPS): to assess risk of relapse for diffuse large and high grade B-cell lymphomas.

One point is scored for each of the following variables:

- Age >60 years
- Serum LDH >upper limit of normal
- Performance status 2-4
- Ann-Arbor Stage III-IV
- >1 extra-nodal site of disease

Score 0-1 = low risk

Score 2 = low-intermediate risk

Score 3 = high-intermediate risk

Score 4-5 = high risk

The International Non-Hodgkin's Lymphoma Prognostic Factors Project., A Predictive Model for aggressive Non-Hodgkin's Lymphoma. N. Engl. J. Med, 1993. 329(14): p. 987-984.

### **Chronic Lymphocytic Leukaemia (CLL)**

See guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Hallek et al, Blood 2008, 111:5446-5456.

### **Myeloma**

See consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Rajkumar et al, Blood. 201; 117(18): 4691–4695.

## Appendix 4. Disease terms

You may come across the following terms to describe the disease status of the patient. The disease status determines the aims of the trial and the outcome measures chosen.

Term	Meaning
Local	Confined to the organ where the tumour originated
Nodal	Cancer that has extended into the local lymph nodes
Loco-regional	Tumour in index organ, local nodes and sometimes adjacent structures
Contralateral	Cancer that is present on the opposite side e.g. cancer in the right breast following a diagnosis in the left breast
Metastatic	Tumour that has spread to other organs and/or distant lymph nodes
Remission	A decrease in or disappearance of signs and symptoms of cancer. In partial remission some, but not all, signs and symptoms of cancer have disappeared. In complete remission all signs and symptoms of cancer have disappeared, although cancer may still be in the body.
Refractory	Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment. Also called resistant cancer.
Relapse	Cancer that has been detected after complete removal by surgery or complete response, or period of complete remission following other previous treatments.

### RECIST terminology for response (following radiotherapy or drug therapy)

The main criteria for assessing response in solid tumours is the RECIST criteria, see p5.

Response to treatment	Definition
Complete Response (CR)	Disappearance of all tumour lesions and no new lesions
Partial Response (PR)	At least 30% decrease in longest diameter of target lesions from baseline, no progression of non-target lesions and no new lesions
Stable Disease (SD)	Neither increase or decrease sufficient for PR or PD, and no new lesions
Progression (PD)	At least 20% increase in longest diameter of target lesions from smallest measurement, progression of non-target lesions or new lesions

The criteria are used to define progression and response. In some trials both CR & PR are combined to describe response.

These criteria have been modified for use with immunotherapies where tumour size may not correlate as well with response to treatment, see p6.

## Appendix 5. Performance status

Patients are frequently selected on the basis of their performance status as this reflects the burden of disease and their ability to tolerate treatment. Two commonly used criteria are given below. The ECOG system is referred to in the NCI Common Toxicity Criteria.

Grade	Eastern Cooperative Oncology Group (ECOG) & World Health Organisation (WHO)
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Oken et al. Am J Clin Oncol 5:649-655, 1982

Grade	Karnofsky Performance Status
100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0%	Death

The clinical evaluation of chemotherapeutic agents in cancer; In Evaluation of chemotherapeutic agents. Karnofsky & Burchenal. MacLeod CM, editor. New York: Columbia University Press; 1949. pp. 191–205.

## Appendix 6. Treatment terms

The type of cancer treatment and setting influences the design and management of a cancer trial.

**Primary:** Usually the first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, primary treatment is the most effective treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead. In metastatic cancer it may be called first-line therapy.

**Adjuvant:** Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy e.g. drugs or radiotherapy given after surgery to eliminate any metastatic cells and reduce the risk of cancer recurring.

**Neo-adjuvant:** Treatment given as a first step to shrink a tumor before the main (primary) treatment, which may be surgery or radiotherapy. Examples of neo-adjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy. It may reduce the extent of surgery or improve the chance of a favourable response to radiotherapy

**Consolidation:** Treatment given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body to improve the time to relapse or length of remission. It may include radiotherapy, a stem cell transplant, or drugs. Also called intensification therapy and post remission therapy.

**Salvage:** Treatment that is given after the cancer has not responded to other treatments (resistant or refractory disease) in an attempt to regain a remission

**Maintenance:** Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time. Maintenance chemotherapy may be given in lower doses than during primary treatment

**Palliative:** Treatment given to relieve the symptoms, improve quality of life and reduce the suffering caused by cancer. Palliative cancer therapies are given together with other cancer treatments, from the time of diagnosis, through treatment, survivorship, recurrent or advanced disease, and at the end of life.

**Best supportive care:** The goal of best supportive care is to prevent or treat as early as possible the symptoms of cancer, side effects caused by treatment, and psychological, social, and spiritual problems related to a disease or its treatment. Also called palliative care, and symptom management.

**First-line:** The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead. Also called induction therapy, primary therapy, and primary treatment.

**Second-line:** Treatment that is given when initial treatment (first-line therapy) doesn't work, or stops working.

NB. based on NIH NCI Dictionary of terms

# Appendix 7. Additional sources of information

## Books

### Cancer biology, tests and treatment

- A Beginner's Guide to Targeted Cancer Treatments. Vickers. Wiley 2018
- Cancer and its Management, Tobias & Hochhauser, 7th Ed, Wiley, 2010
- Cancer Demystified: Cells, Tissues & Cancer. O'Halloran, independently published, 2017
- Essential Haematology, AV Hoffbrand and Pettit, 1 7th Ed, Wiley, 2015
- The Emperor of All Maladies, Mukherjee. Fourth Estate Ltd, 2011
- UICC TNM Classification. 8th Ed, Wiley, 2016

### Books on trial methodology and practice

- Cancer Clinical trials, Buyse et al, Oxford 1990
- Clinical Trials in Cancer, principles & practice, Girling et al, Oxford 2003
- Phase I Cancer Clinical Trials, Eisenhauer et al, 2nd edition, Oxford 2015
- Sympathy for the Devil; the true story of a cancer biotechnology and its small biomedical company and its battle against disease, destruction and death. Gary Acton

## Training Courses

- CR UK & UCL CTC: runs a variety of training courses as part of their new starters training programme. [www.ctc.ucl.ac.uk/Training.aspx](http://www.ctc.ucl.ac.uk/Training.aspx).
- David O'Halloran Consultancy [www.ohconsultancy.co.uk/](http://www.ohconsultancy.co.uk/). David delivers face to face courses around the country and webinars.
- Elaine Vickers, Science Communicated <http://sciencecommunicated.co.uk/>. Elaine regularly delivers courses through the Royal Marsden and Christie hospitals and she has collaborated with CR UK to develop a free online course on targeted treatments.
- [www.futurelearn.com/courses/targeted-cancer-treatments-on FutureLearn](http://www.futurelearn.com/courses/targeted-cancer-treatments-on-FutureLearn).
- European Institute of Oncology via ecancer <http://ecancer.org/>. Provides free e-learning courses to the oncology community. Resources cover a variety of topics via registration on their site which records your learning.
- National Cancer Registration and Analysis Service - E-Learning programme of around 40 modules accredited by the Institute of Healthcare Management. 'Understanding cancer' series [www.ncin.org.uk/cancer\\_information\\_tools/training/default.aspx](http://www.ncin.org.uk/cancer_information_tools/training/default.aspx).
- NIHR Cancer Researchers Introductory Course. This one-day course is delivered in some Clinical Research networks around the UK and gives an introduction to cancer diagnosis and treatment.