

The background of the lower half of the page is a photograph of a diverse group of people in a professional setting, likely a conference or meeting. The image is overlaid with a semi-transparent teal filter. The people are engaged in conversations, some looking at documents or devices. The overall atmosphere is one of professional collaboration.

# The Guide to Efficient Trial Management

*Effectively managing clinical trials*

The Fifth Edition (2016) of the Guide to Efficient Trial Management was produced by an appointed Editorial Board and a panel of reviewers all of whom are trial managers on behalf of the UK Trial Managers' Network.

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Please note that guidance can change, so please use the relevant links to ensure you have the most up-to-date information.

## Devolved nations

While most of the legislation and guidance provided in this guide is applicable to Trial Managers across the UK, please note that devolved administrations within the UK may have some additional regulatory requirements and guidelines. Please refer to the relevant organisations for additional information (NHS Research Scotland, National Institute for Social Care and Health Research Wales or Health & Social Care in Northern Ireland).

## Disclaimers

This guide has been developed for general information and education purposes only and does not constitute legal advice or opinions as to the current operative laws, regulations or guidelines of any jurisdiction.

In addition, because new standards and guidelines are issued on a continuing basis, the guide is not an exhaustive source of all current applicable laws, regulations and guidelines relating to interventional and non-interventional trials. While reasonable efforts have been made to assure the accuracy and completeness of the information provided, Trial Managers and other individuals should check with the relevant research governance bodies, for example the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committees (RECs), and Research and Development (R&D) departments, before and during trials.

# Commonly used terms

**ACORD** Guidance that provides a framework for the NHS and its partners to identify, recover and attribute the costs of health and social care research and development

**Administration of Radioactive Substances Advisory Committee (ARSAC)** The body from which researchers who want to administer radioactive medicinal products to human subjects need to obtain approval before NHS R&D permission.

**Amendment** A written description of a change or formal clarification. Substantial amendments (see below) to protocol or participant information/consent require REC, R&D and MHRA approval. Non-substantial amendments should be 'notified' to REC, R&D and MHRA (for CTIMPs and non-CE marked devices).

**ATMP** Advanced Therapy Medical Products

**CAG** Confidentiality Advisory Group

**Case Report Form (CRF)** Data collection tool provided by a sponsor in which the clinical data are recorded for each participant, such as weight, laboratory results and symptoms.

**Chief Investigator** The Lead Investigator with overall responsibility for the research. In a multisite trial, the Chief Investigator has coordinating responsibility for research at all sites. The Chief Investigator may also be the Principal Investigator at the site in which they work. In the case of a single-site trial, the Chief Investigator and the Principal Investigator will normally be the same person, referred to as Principal Investigator.

**Clinical Research Network (CRN)** The NIHR CRN supports researchers and the life-sciences industry in developing, setting up and delivering high quality research to time and target in the NHS in England. Health service infrastructure (eg research support staff such as research nurses and research support services such as pharmacy, pathology and radiology) can be provided to eligible trials. The NIHR CRN comprises 15 Local Clinical Research Networks (LCRNs).

**Clinical Trials Authorisation (CTA)** The regulatory approval for a clinical trial of a medicinal product issued by the MHRA.

**Clinical Trials Unit (CTU)** Specialist units that have been set up with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. They have the capability to provide specialist expert statistical, epidemiological and other methodological advice and coordination to undertake successful trials.

**Competent Authority** Organisation approving the testing of new drugs/devices or approving the marketing licences. In the UK, this is the MHRA.

**CONSORT** Consolidated Standards of Reporting Trials. An evidence-based, minimum set of recommendations for reporting randomised controlled trials.

**CTIMP** Clinical Trial of an Investigational Medicinal Product

**DSUR** Development Safety Update Report

**European Clinical Trials Database (EudraCT)** A database of all clinical trials in Europe, held since 1994 in accordance with EU directive 2001/20/EC.

**Excess Treatment Costs (ETC)** The difference between standard treatment and the experimental treatment cost.

**Good Clinical Practice (GCP)** A set of ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. For CTIMPs the standards are dictated by the Medicines for Human Use Clinical Trials Regulations; for non CTIMPs MRC standards are usually followed. In respect of trials for regulatory submissions the ICH GCP standards apply.

**Good Manufacturing Practice (GMP)** A quality assurance standard for producing investigational medicinal products.

**Gene Therapy Advisory Committee (GTAC)** The ethics committee for clinical studies using genetically modified products; usually no REC approval is required.

**Health Research Authority (HRA)** The purpose of the HRA is to protect and promote the interests of patients and the public in health research. The HRA works closely with other bodies, including the MHRA and NIHR, to create a unified approval process and to promote proportionate standards for compliance and inspection within a consistent national system of research governance.

**Health and Social Care Information Centre (HSCIC)** The provider of information, data and IT systems for health and social care in England.

**Indemnify** To secure (someone) against legal responsibility for their actions.

**Information Services Division (ISD) Scotland** A division of National Services Scotland, part of NHS Scotland. ISD provides health information, health intelligence, statistical services and advice that support the NHS in progressing quality improvement in health and care and facilitates robust planning and decision-making.

**Insurance** A practice by which an insurance company provides an indemnity to compensate another party for their specified loss, liability, damage, illness or death; in return for payment of a premium.

**Integrated Research Application System (IRAS)** A single, web-based system for completing applications for the permissions and approvals required for health and social care research in the UK. The various applications can be submitted for this single system (includes REC, R&D, MHRA, Gene Therapy Advisory Committee).

**Investigational Medicinal Product (IMP)** An unlicensed new drug, or an existing drug tested outside its licence, or existing drugs tested against each other for their efficacy/safety.

**Investigator** Researcher conducting the trial; those researchers leading the team are referred to as Chief Investigator or Principal Investigator.

**Investigator Brochure** A compilation of clinical and pre-clinical pharmacological/biological data relevant to the use of those particular IMPs in human subjects (one single brochure must be used as the Reference Safety Information for all trials using the same IMP).

**Investigator Site File (ISF)** A file designed for use in organising and collating all essential documentation required to conduct a trial in accordance with the principles of GCP and the applicable regulatory requirements such as REC approval letter/correspondence, MHRA approval, blank CRF, staff CVs, delegation of duties log.

**INVOLVE** A national advisory body funded by the NIHR to support public involvement in NHS, public health and social care research.

**ISO 14155 A** European standard for the organisation and documentation of clinical trials for medical devices.

**ISRCTN** International Standard Randomised Controlled Trial Number. A simple numeric system for the identification of randomised controlled clinical trials worldwide. Allows the identification of trials and provides a unique number that can be used to track all publications and reports resulting from each trial.



**Medicines and Healthcare products Regulatory Agency (MHRA)** The organisation responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe.

**Medicines for Human Use (Clinical Trials)** SI 2004:1031 and subsequent amendments 2006:1928, 2006:2984, 2008:941, 2009:1164, and 2010:1882 are the UK Statutory Instruments translating EU directives 2001/20/EC and 2005/28/EC into UK law, laying down the legal requirements for conducting CTIMPs in the UK.

**Monitor** The person designated by the sponsor to perform site visits and conduct the monitoring process; for example, to check whether or not there are any deviations from the protocol and that all source data are correctly transferred into the Case Report Forms.

**Multicentre** A trial conducted according to a single protocol but carried out at more than one site and by more than one investigator; one Chief Investigator oversees several local Principal Investigators.

**National Health Service Research Design Service (NHS RDS)** An NHS initiative which provides design and methodological support to health and social care researchers across England to develop grant applications to the NIHR and other open national peer-reviewed funding programmes.

**National Institute for Health and Care Excellence (NICE)** Provides national guidance and advice to improve health and social care. NICE's role is to improve outcomes for people using the NHS and other public health and social care services by producing evidence-based guidance and advice for health, public health and social care practitioners; developing quality standards and performance metrics for those providing and commissioning health, public health and social care services; and providing a range of information services for commissioners, practitioners and managers across the spectrum of health and social care.

**National Institute for Health Research (NIHR)** Established by the Department of Health for England in 2006 to provide the framework through which the Department of Health can position, fund, maintain and manage the research, research staff and infrastructure of the NHS in England. The mission of the NIHR is to maintain a health research system in which the NHS supports outstanding individuals working in world-class facilities conducting leading-edge research focused on the needs of patients and the public.

**National Research Ethics Service (NRES)** Umbrella organisation responsible for all RECs across the UK (incorporated into HRA in 2013).

**NHS Information Centre for Health and Social Care (NHS IC)** England's central, authoritative source of essential data and statistical information for frontline decision-makers in health and social care.

**Non-substantial amendments** Changes to the details of a trial that have no significant implications for the subjects or the conduct, management or scientific value, of the trial (sometimes referred to as administrative amendments).

**Office for National Statistics (ONS)** The UK's largest independent producer of official statistics and the recognised national statistical institute of the UK.

**Participant/Patient information leaflet/sheet** An information leaflet given to those who have been invited to participate in a trial. The leaflet is designed to provide the potential participant with sufficient information to allow that person to make an informed decision on whether or not they want to take part.

**Patient and Public Involvement (PPI)** The process whereby research is carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them; for example, members of the public, such as patients, service users and carers, may comment on or develop research materials or become members of Trial Steering Groups. Terms used can vary between PPI, public involvement or sometimes as Patient Carer and Public Involvement (PCPI).



**Personal Demographics Service** The national electronic database of NHS patient demographic details such as name, address, date of birth and NHS Number.

**Pilot study** A version of the main study that is run in miniature to test whether the components of the main study can all work together.

**External pilot** A stand alone piece of work planned and undertaken independently of the main trial. The data from an external pilot might be analysed but set aside.

**Internal pilot** Set up with the intention of being incorporated into the main trial and data from the internal pilot phase may contribute to the final analysis.

**Portable Appliance Testing (PAT)** The term used to describe the examination of electrical appliances and equipment to ensure they are safe to use.

**Principal Investigator** The lead person at a single site designated as taking responsibility within the research team for the conduct of the trial.

**Randomised Controlled Trial (RCT)** A trial in which two or more forms of treatment/care are compared; the participants are allocated to one of the forms of care in the trial, in an unbiased way.

**Research and Development (R&D)** Often the name of the department within NHS hospitals giving NHS permission to conduct research on those facilities with patients/staff.

**Research Ethics Committee (REC)** The body authorised by NRES to review documents for research taking place in the NHS or social services. Some RECs specialise in clinical trials or topics such as research in children. See NRES website for more detail and other types of research. All research in NHS/social services must be reviewed by a UK REC.

**Research Governance Framework (RGF)** Research governance concerns setting standards to improve research quality and safeguard the public. The Health Research Authority (HRA) is currently developing a replacement for the Research Governance Framework in England.

**Research Passport** A system for Higher Education Institution (HEI)-employed researchers/postgraduate students who need to undertake their research within NHS organisations. The Research Passport provides evidence of the pre-engagement checks undertaken on that person in line with NHS Employment Check Standards [including Criminal Records Bureau (CRB) and occupational health].

**Serious Adverse Event (SAE)** An untoward occurrence that results in death; is life-threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; or consists of a congenital anomaly or birth defect. There are slight differences in definition for CTIMPs and non CTIMPs; the CT Regulations should be referred to for CTIMPs.

**Site** The NHS organisation in which trial activities and assessment are performed or the location(s) where trial-related activities are actually conducted. Each site/trust needs to give R&D approval (permission).

**Site Initiation Visit (SIV)** Often the point when sites are trained in trial processes. The PI and as many members of the research team as possible should attend, including representation from relevant supporting departments (eg pharmacy).

**Site-Specific Assessment** An assessment performed to establish the suitability of a Principal Investigator and a site for the conduct of research; site-specific assessments will be performed by the participating CRN for each research site (NHS organisation) using an SSI (Site-Specific Information) form available in IRAS.

**Source data verification** Checking the original data record, such as laboratory reports or patient medical notes, against what was transferred onto the CRF database.

**Standard Operating Procedure (SOP)** Detailed written instructions designed to achieve uniformity of the performance of a specific function.

**Standard Protocol Items Recommendations for Interventional Trials (SPIRIT)**

Recommendations for the minimum set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol.

**Statutory instrument (SI)** These are documents that define UK law on a specific topic; for example the SI (2004/1031) The Medicines for Human Use (Clinical Trials) Regulations.

**Substantial Amendment** A change to the terms of the approval, given by either the competent authority (MHRA in the UK) or the Research Ethics Committee, or a change to the protocol or any other document submitted with the applications, which significantly affects one of the following: (i) the safety or physical or mental integrity of trial participants; (ii) the conduct or management of the trial; (iii) the scientific value of the trial; or (iv) the quality or safety of any investigational medicinal product used.

**Summary of product characteristics (SmPC)** A smaller version of an Investigator Brochure with details on pharmacological effects and side effects, but issued for a product that already holds a marketing licence.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)** A serious adverse reaction that is unexpected (i.e. its nature and severity is not consistent with the known information about that product from the Investigator's Brochure or the SmPC) and suspected, as it is not possible to be certain of a causal relationship with the IMP.

**Trial Master File (TMF)** File containing essential documents held by the Chief Investigator/ Sponsor.

**UK Clinical Research Network (UKCRN)** Clinical Trials Unit Network Registered CTUs that have been awarded UKCRC Registration and provided evidence to an international panel of experts of their capability to centrally coordinate multicentre trials (i.e. having overall responsibility for the design, development, recruitment, data management, publicity and analysis of a portfolio of trials), and that they have established robust systems to ensure conduct and delivery of trials to the highest quality standards.

**Virement** (to vire) The transfer of surplus funds from one account to cover a deficit in another.

# Introduction

## Background

The first edition of the TMN Guide to Efficient Trial Management was produced in March 2000. The fourth edition was last produced in 2014. It is from this fourth version that the current group of volunteers working within trials research from all over the UK have come together to produce this new edition.

## Purpose

This Guide is intended as a reference tool, providing pragmatic advice and guidance to all those involved in the management of trials.

It describes the process of managing trials and gives an overview of the trial management framework, both legal and operational, providing practical hints, tips and references to external resources. It documents information, practical experience, research, analysis and reflection for the effective and efficient management of trials.

## Application

This Guide contains useful information, guidance and references, and tools and resources. It is aimed at both novice and experienced Trial Managers, and can be used as an induction tool with newly appointed staff. It may also be useful to students aspiring to pursue a career in trial management.

## Scope

The main focus is predominantly late-phase, interventional, academic trials. As many aspects of trial management apply across all trials, Trial Managers of early Phase I and Phase II trials may also find aspects of this guide useful and applicable to their work.

One of the main objectives was to produce an inclusive resource, relevant to trials of a wide range of interventions and not limited to Clinical Trials of Investigational Medicinal Products (CTIMPs).

The content of the Guide has potentially wider applicability and relevance to the management of other well-designed studies such as case-control and cohort designs.

## Use of the Guide

The content of this document can be accessed, printed and downloaded in an unaltered form by Trial Managers and other research professionals, with copyright acknowledged, for personal study that is not for direct or indirect commercial use.

The Guide can also be used by Higher Education Institutions as a teaching and training aid, subject to appropriate recognition of the UKTMN.

## Limitations of the Guide

This Guide is not a legal document, nor is it intended to be comprehensive or exhaustive. It consolidates into one document key information, available evidence and practical experience relevant to the field of trial management.

# Section 1 Understanding randomised trials

## 1.1 Why do a randomised trial?

Assessment of the risks and benefits of a new treatment or other intervention needs to be based on reliable evidence. The most reliable evidence is best obtained by carrying out randomised controlled trials to compare outcomes of similar groups of participants who receive either the new intervention or the current standard intervention or, if there is no current standard, a placebo (or no active treatment). These trials need to be large enough to estimate the effects of an intervention or procedure with a high level of confidence.

The group that does not receive the intervention being evaluated is called the control group. This group may receive the standard intervention (current best practice/treatment as usual) or, if there is no standard intervention available, no intervention or a placebo (dummy) intervention.

Ethically, equipoise should exist for a randomised trial to be undertaken; that is, genuine uncertainty about the additional benefits and risks of the new intervention over the current standard intervention.

Randomised trials are the gold standard<sup>1</sup> as they aim to minimise potential bias in the estimation of the effect of the intervention. The two primary ways of minimising bias are randomisation and blinding. Chance effects are minimised by including large enough numbers of participants.

## 1.2 Randomisation and methods

### Randomisation

In a randomised trial designed to evaluate a novel intervention versus control with equal numbers in each group (1:1), random allocation of the trial intervention gives all participants the same chance of receiving the new intervention or the control intervention. It is fairly uncommon but some trials have unequal treatment ratios of 1:2 or 1:3.

Allocation is independent of the characteristics of the participants, unless the allocation uses stratification or minimisation (see randomisation methods below) or preferences or prejudices of the investigator and participants. This can be achieved only if concealment of intervention allocation is secure such that the investigator and participants are ignorant of, and unable to predict, the next intervention allocation.

### Randomisation methods

**Simple randomisation** – allocation decided by (the equivalent of) a random number table, a computer program or the toss of a coin.

**Minimisation** – improves balance between the groups in terms of important characteristics, especially in small samples. It is based on the idea that the next participant to enter the trial is more likely to be allocated the intervention that would minimise the overall imbalance of selected characteristics between the groups at that stage.

**Blocked (or restricted) randomisation** – interventions assigned randomly within blocks to ensure balance within the blocks. Blocks can be of any size, but a multiple of the number of intervention groups is logical. The block size should be small and variable, and unknown to the investigators, to prevent predictability and maintain concealment.

**Stratified randomisation** – gives a balance within subgroups defined by important variables (prognostic factors) such as centre or country in a multicentre trial. Blocked randomisation is often used within each stratum. Stratification is not feasible for small studies or where many variables exist.

**Cluster randomisation** – the unit of randomisation is not the individual participant being studied but groups of participants, for example, clusters, GP patients or a village community. This design is particularly appropriate when the intervention is at a group level. The overall sample size required is larger because the analysis is based on the cluster unit.

### 1.3 Blinding (also known as masking)

- Double blind – both investigator and participant are unaware of the intervention allocation.
- Single blind – either the participant or the investigator is unaware of the intervention allocated.

It is impossible to blind the investigator in some trial designs (eg the surgeon in a surgical trial). When only single blinding can be achieved, it is usually the participant who is 'blind'.

Whether or not it is possible to blind the participant and the care-giver, the outcomes should be well defined and objective and the person assessing the pre-specified outcomes should, whenever possible, be unaware of or blind to the intervention allocated. The trial team should (where possible) also remain blind to avoid bias.

### 1.4 Placebos

Placebos are dummy interventions often used in drug trials but sham treatments may also be used in non-drug studies. Although more difficult to organise in non-drug trials of complex interventions, placebos are sometimes both feasible and desirable in this setting. If there is no existing standard intervention, then giving the control group no active intervention is ethical, and blinding can be achieved by use of a placebo. The placebo must be pharmacologically inactive but identical in appearance and taste to the active intervention.

#### Double-dummy placebo

In many trials where there is an existing treatment for a disease, it is not appropriate or ethical to withhold treatment from the control group and, therefore, the comparison is between the new treatment and the standard treatment. In order to blind both the participants and the clinical team, various methods can be adopted. Ideally, the new treatment and standard treatment would be prepared in such a way that they cannot be distinguished, except by laboratory analysis. This is often not feasible as the two preparations may have very different characteristics. A double-dummy technique is often used in these circumstances. Placebo preparations for both treatments are required so that the group allocated to the new treatment receives a placebo matched to the standard treatment, and those allocated to the standard treatment receive a placebo matched to the new treatment. One disadvantage of this approach is that participants have to have extra trial treatments and this may reduce compliance. Involving the public (eg patients, service users and/or carers) in the trial design can help in anticipating the acceptability of the proposed methods.

### 1.5 Sample size

The planned sample size or number of participants required is calculated to ensure a high chance of detecting a clinically important difference at a specified level of statistical significance if one truly exists. In order to calculate the sample size, the number of primary events (or event rate), or summary measure of the outcome (eg mean), in the control group must be known or estimated reasonably accurately so that a realistic estimate of the size of effect of the intervention can be made. It is usually prudent to have a larger than required sample size to allow for dropouts, poor adherence and/or loss to follow-up. The sample size must be pre-specified but may be reviewed during the course of a trial, especially if event rates are not well known. The sample size provides the overall recruitment target for the trial.

### 1.6 Power

The probability that a trial of a given size will detect a clinically important difference at a given level of significance, if a true difference of a certain size exists, is known as the statistical 'power'. The greater the power (typically 80% or 90%), the more certain it is that the trial will be able to detect the difference if it exists, but also the larger the sample size needed.

### 1.7 Confidence intervals

A confidence interval is a range of values which would contain the true effect size; commonly a 95% confidence interval is used. This means if we were to repeatedly sample from the same population and obtain a confidence interval, 95% of these cases would contain the true effect size. Alternatives such as 80%, 90% and 99% may also be used. If you want more confidence that an interval contains the true value, you widen the interval (ie a 99% confidence interval is wider than a 95% interval).



## 1.8 Confounding

Confounding occurs when the interventions to be examined are not the only differences between the groups being compared, so that differences in outcome may not be due to the intervention. One example of this would be when investigating the relationship between diet and BMI. Life style/exercise would be an important confounding factor, as exercise may be associated independently with the outcome (BMI).

## 1.9 Outcomes

A key element in the design and management of trials is the identification and agreement of trial outcomes. There are typically many outcomes relevant to the research question, but it is normal practice for one of these to be classed as the primary outcome with the others being classed as secondary. It is helpful to involve the public in the design of the trial (eg to assist with the identification of outcomes).

The primary outcome is the most important outcome. It should be an important outcome with regard to addressing the research question. The sample size is determined with respect to the primary outcome. As a consequence, the primary outcome needs to be one that can be readily assessed and that leads to a feasible sample size. In some circumstances, there may be more than one primary outcome; this will have been considered in trial development and with significant input from the trial statistician. Secondary outcomes chosen should be sufficient to address all relevant aspects of the intervention, but care should be taken to avoid data overload, which is burdensome for both participants and investigators.

A description of all the outcomes should be included in the trial protocol together with a description of how, when and by whom data will be collected. There are various types of outcomes including clinical outcomes, participant-reported health-related quality of life and health economic measures. The data can be collected by various means, such as questionnaires to participants to collect patient-reported outcomes and clinical information collected from GPs/clinical staff at participating sites. Timing of outcome data collection also requires agreement and management – for example, at which time points, such as baseline and long-term follow-up and from which sources and by whom. A useful resource is the work being done by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative - [www.comet-initiative.org/](http://www.comet-initiative.org/).

Outcome data should be collected and assessed in a way that reduces bias and maximises response.

## 1.10 Types of trials

The Phase I to Phase IV classification is most often applied to drug trials.

### Phase I: first test in humans

Phase I trials are the first stage of testing in humans. Normally, a small group of 20–100 healthy volunteers (HV) will be recruited. This phase is designed to assess safety (pharmacovigilance), tolerability, pharmacokinetics and pharmacodynamics. These trials are often conducted in a trial clinic, where the subject can be observed by full-time staff.

Phase I trials:

- aim to establish safe/tolerable levels.
- aim to establish initial pharmacokinetics.
- usually include healthy volunteers, who may be paid but may be patients who are not usually placebo controlled.

There are lots of different types of Phase I trials – Single Ascending Dose (SAD), Multiple Ascending Dose (MAD), food effect, drug-drug interaction etc. These trials are normally conducted in a Phase I Unit.

### Phase II

Phase II trials are designed to assess how well the drug/intervention works, as well as to continue Phase I safety assessments in a larger group of participants and patients. When the development process fails, this usually occurs during Phase II trials when the drug/intervention is discovered not to work as planned, or to have toxic effects.

Normally conducted in a group of patients with very specific inclusion/exclusion criteria when it comes to the disease being monitored. Can also include HVs if still assessing safety.



Phase II is sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements, how much should be given and whether the drug has any effect at all. Phase IIB is specifically designed to study efficacy and how well it works at the prescribed dose(s). Some Phase II trials combine Phase I and Phase II, and test both efficacy and toxicity.

Phase II feasibility trials are often used to resolve uncertainties regarding the design and conduct of the main Phase III trial. Issues such as recruitment, randomisation and follow-up rates, adherence to interventions and choice of outcome measures, including gaining empirical evidence for the main trial sample size calculation, are frequently investigated in a feasibility study. The numbers of eligible patients are also sometimes assessed at this stage to assist planning of the main trial. The feasibility trial will have different end points from the main trial, focused around the uncertainties of design and conduct of the Phase III trial, while a pilot trial is a smaller version of the main trial and will have the same end points as the Phase III trial.

Phase II trials:

- include participants with the disease or condition under investigation.
- aim to provide evidence of activity and additional evidence of safety.
- aim to define dosage and regimen.
- may or may not be randomised and/or placebo-controlled.

### Phase III

Phase III trials are randomised controlled multicentre trials on large patient groups of 300–3000 or more depending on the disease/medical condition studied. The patients have a less stringent inclusion/exclusion criteria to provide data on how the drug works for the whole spectrum of patients with that disease and are aimed at being the definitive assessment of how effective the drug/intervention is, in comparison with current gold standard treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

Phase III trials:

- include participants with the disease or condition under investigation.
- aim to assess the efficacy, safety and, therefore, the balance of risks and benefits.
- compare benefits and side effects with those of standard treatment or a placebo or both.

### Phase IV: 'later efficacy' post-marketing surveillance trials

Phase IV trials evaluate medicines/interventions that are already available for doctors to prescribe, rather than new developments. Phase IV trials include participants with the disease or condition under investigation.

The main reasons for conducting Phase IV trials are to find out:

- more about side effects and safety in a larger population.
- what the long-term risks and benefits are by conducting long-term follow-up.
- performance when used in a broader population or in a combination of treatments.

### Phase V: comparative effectiveness and community-based research

Phase V is a term used increasingly in the translational research literature to refer to comparative effectiveness research and community-based research. It is used to signify the integration of new treatments into widespread health practice.

### Cluster randomised trials

Trials of behavioural interventions or public health interventions, for example school-based interventions to improve physical activity, are often delivered with a cluster randomised trial design. The unit of randomisation is the school, not the individual, as that is how the interventions would be given subsequently, and this design also helps to reduce contamination of control participants taking up the intervention. Usually these trials have to be larger in size than the equivalent trial with individual randomisation.

### Feasibility study

Research undertaken before the main trial starts in order to answer the question 'can this study be done?'. Feasibility studies do not evaluate the outcome of interest.

### Pilot study

A version of the main trial run in miniature to test whether the components of the main trial can all work

together. A pilot study reflects the main trial in many components, including an assessment of the primary outcome.

### **Efficacy versus effectiveness**

An efficacy trial is designed to establish whether an intervention produces the desired clinical outcome under optimal conditions, while an effectiveness trial tests whether the procedure works under usual/ everyday circumstances (pragmatic).

# Section 2 National infrastructure

## 2.1 UK Clinical Research Collaboration (UKCRC)

The UKCRC was formed largely in response to the publication of key reports from the Academy of Medical Sciences (AMS) and from the Bioscience Innovation and Growth Team (BIGT) both of which highlighted a number of issues that needed to be addressed in order to strengthen clinical research in the UK.

Established in 2004, the UKCRC brings together the major stakeholders that influence clinical trials research in the UK including the main funding bodies, government, charities, academia, the NHS, regulatory bodies, industry and consumers.

The Collaboration promotes a strategic approach to identifying opportunities and obstacles to clinical research and works collaboratively to resolve issues. The ultimate aim is patient benefit by improving national health and increasing national wealth. Key areas of work relating to Trial Management are highlighted below. More information on all areas of activity can be found on the UKCRC website at [www.ukcrc.org](http://www.ukcrc.org).

## 2.2 UKCRC Registered Clinical Trials Unit Network

The UKCRC identified Clinical Trials Units (CTUs) as an important element of the UK-wide clinical trials infrastructure. CTUs are specialist units that have been set up with a specific remit to design, conduct, analyse and publish trials and other well-designed studies. Most CTUs will have expertise in the coordination of trials involving investigational medicinal products (IMPs), which must be conducted in compliance with the UK/EU legislation<sup>2</sup> relating to the conduct of clinical trials.

A UKCRC Registration Process was established for CTUs responsible for coordinating multicentre clinical studies with the intention of improving the quality and quantity of available expertise to carry out clinical trials. To achieve UKCRC Registration, CTUs are required to provide evidence to an international panel of experts of their capability to centrally coordinate multicentre trials, i.e. having overall responsibility for the design, development, conduct, data management, publicity and analysis of a portfolio of trials, and that they have established robust systems to ensure conduct and delivery of trials to the highest quality standards.

The Network comprises all UKCRC Registered CTUs and helps to provide a national voice for CTUs in response to consultations. The Network also coordinates a number of working groups in key areas such as working with industry, efficient trial conduct, insurance, core infrastructure and resources and operational groups for Quality Assurance, Statistics and Information Systems.

Further details about the UKCRC Registered CTU network functions, services and Working Groups can be found at the UKCRC-registered CTUs network website [www.ukcrc-ctu.org.uk/](http://www.ukcrc-ctu.org.uk/).

## 2.3 UK Clinical Research Network (UKCRN)

Clinical research networks (CRNs) have been established across the UK to provide the infrastructure to support high quality clinical studies across all areas of disease and clinical need. Strategic oversight is provided by the UKCRC ensuring the CRNs across the UK work together in an integrated manner to share experiences, develop joint initiatives and promote partnership and UK-wide working wherever possible.

The networks are funded by the relevant countries' health department and, although the exact structure of the network varies between countries, all provide the following elements for eligible studies:

- Advice to researchers on the feasibility of studies, to ensure that they can be practically delivered through the NHS.
- Funding and supporting an infrastructure of trained research support staff in the NHS, so that researchers have access to experienced people to provide the NHS service support required for research.
- Maintaining a knowledge base of NHS sites and their research strengths and capabilities, for researchers to access as a resource.
- Monitoring the numbers of patients participating in individual trials, and offering a trouble-shooting service to help studies that are falling behind with their recruitment targets.

More information about which studies are eligible for Network support can be found at [www.crn.nihr.ac.uk/can-help/funders-academics/nihrcrn-portfolio/which-studies-are-eligible-for-clinical-research-network-support/](http://www.crn.nihr.ac.uk/can-help/funders-academics/nihrcrn-portfolio/which-studies-are-eligible-for-clinical-research-network-support/).

When planning a new study it is helpful to liaise with the local network contact to discuss the study and resource implications to ensure network support in the longer term. If the CI is based in a different geographical location to the trial manager, it is normal to have these discussions with the network where the CI is based. During the course of the study the Network can be a valuable contact point to resolve site specific issues such as low recruitment or data return rates. Further information regarding the CRNs and related infrastructure can be found on the relevant country-specific host websites:

In England the Network is hosted by the National Institute for Health Research which also funds and commissions research alongside providing research infrastructure and training. There are 15 Local Clinical Research Networks, contacts for each can be found at: [www.crn.nihr.ac.uk/](http://www.crn.nihr.ac.uk/).

In Scotland the Network is hosted by the Chief Scientist Office: [www.cso.scot.nhs.uk/nrs/](http://www.cso.scot.nhs.uk/nrs/).

In Northern Ireland the Network is hosted by the Public Health Agency's (PHA) Health and Social Care Research and Development (HSC R&D) Division: [www.nicrn.hscni.net/](http://www.nicrn.hscni.net/).

In Wales the Network is hosted by Health and Care Research Wales: [www.healthandcareresearch.gov.wales/research-infrastructure/](http://www.healthandcareresearch.gov.wales/research-infrastructure/).

## 2.4 Health Research Authority (HRA)

The HRA was established in 2011 with the strategic goal of making the UK a global leader in health research. In order to do this the HRA has various work-themes which cover streamlining research, transparency in research, patient and public engagement in research and working with the devolved nations. In practical terms, the HRA leads on a number of key projects which have an impact on clinical trial delivery, for example, implementation of HRA approval which aligns the Research Ethics Committee (REC) approvals' process with NHS R&D approvals to reduce duplication and create a single 'HRA assessment' and hosting the integrated research application system (IRAS). HRA is also responsible for issuing guidance for research in England, in place of the Research Governance Framework (RGF).

The HRA regularly issues consultations and calls for good practice or evidence in relation to clinical trial conduct and past consultations have included protocol guidance and a template for use in a Clinical Trial of an Investigational Medicinal Product (CTIMP), model Non-Commercial Agreement (mNCA) revisions and seeking informed consent for simple and efficient trials in the NHS.

The HRA website provides up to date information on all areas of work: [www.hra.nhs.uk/](http://www.hra.nhs.uk/).

# Section 3 Regulatory framework for clinical trials

## 3.1 Legislation and guidance

A Trial Manager should ensure that the trials they manage comply with the appropriate national and international standards and guidance, regulations and legislation (see Table 1). In addition, a Trial Manager should adhere to the relevant policies and guidance of his/her employing organisation and the organisation acting as sponsor of the trial.

**TABLE 1** Key legislation, guidance and approvals required

|   | Key legislation and guidance  | Required approvals*   |
|---|---|---|
| <b>All trials</b>   | <ul style="list-style-type: none"> <li>Guidelines for GCP</li> <li>Department of Health Research Governance Framework for Health and Social Care 2005<sup>3</sup></li> <li>Data Protection Act 1998<sup>4</sup></li> <li>Freedom of Information Act 2000<sup>5</sup></li> <li>Mental Capacity Act 2005<sup>6</sup> (non-CTIMPs only)</li> <li>Human Tissue Act 2004<sup>7</sup> (only if collecting human tissues)</li> </ul>   | <ul style="list-style-type: none"> <li>Ethics approval (*NRES/ NHS/HSC Research Ethics Committees)</li> <li>NHS Permissions (NHS/ HSC R&amp;D offices)</li> <li>The NRES is now part of the Health Research Authority (<a href="http://www.hra.nhs.uk">www.hra.nhs.uk</a>)</li> </ul> |
| <b>In addition, for clinical trials of medicinal products</b> | <ul style="list-style-type: none"> <li>Medicines for Human Use (Clinical Trials) Regulations 2004<sup>8</sup> and its amendments 2006a,<sup>9</sup> 2006b,<sup>10</sup> 2008<sup>11</sup> and 2009<sup>12</sup></li> <li>The Medical Devices Regulations 2002<sup>13</sup></li> </ul>   | <ul style="list-style-type: none"> <li>MHRA approval</li> <li>Trials involving non-CE-marked medical devices and CE-marked medical devices used for novel indications</li> </ul>  |
| <b>In addition, for clinical trials of medical devices</b>    | <ul style="list-style-type: none"> <li>The Medical Devices (Amendment) Regulations 2012<sup>14</sup></li> </ul>   | <ul style="list-style-type: none"> <li>MHRA approval</li> </ul>   |
|   | *Depending on the specifics of your trial, you may also require approvals from the following review bodies:   |   |
| <b>Other</b>  | <ul style="list-style-type: none"> <li>Administration of Radioactive Substances Advisory Committee</li> <li>Gene Therapy Advisory Committee</li> <li>Ministry of Justice</li> <li>Health Research Authority (included components of work undertaken formerly by the National Information Governance Board)</li> <li>National Offender Management Service</li> <li>Social Care Research Ethics Committee</li> <li>Expert Advisory Group/the Commission on Human Medicines review for certain first inhuman trials</li> </ul> |   |

## UK Policy Framework for Health and Social Care Research

General principles of good practice to ensure that all research undertaken within NHS health and social care organisations conform to a common set of standards. Similar frameworks exist for England and each of the devolved nations.

More information and guidance is available. See The Health Research Authority website [www.hra.nhs.uk](http://www.hra.nhs.uk).

## World Medical Association ‘Declaration of Helsinki’

A statement of ethical principles for medical research involving human subjects, including identifiable human material and data. There are a number of versions, with the most recent available on the WMA website see [www.wma.net/en/30publications/10policies/b3/](http://www.wma.net/en/30publications/10policies/b3/).

## Good Clinical Practice – all trials

Good Clinical Practice principles are based on providing assurance that the data and reported results of clinical investigations are credible and accurate and that the rights, safety and confidentiality of participants in clinical research are respected and protected. There are a number of different standards which are essentially based on the same set of principles. For CTIMPs the principles set out in the Medicines for Human Use (Clinical Trials) Regulations 2004<sup>8</sup> and the EU Directive on Good Clinical Practice<sup>2</sup> are a legal obligation in the UK/Europe; for non CTIMPs equivalent standards set out by the Medical Research Council are acknowledged as good practice. ICH GCP<sup>15</sup> is an international set of standards which applies to clinical trials for registration purposes.

## Data Protection Act 1998

The Data Protection Act<sup>4</sup> places obligations on those who process information (data controllers) while giving rights to those who are the subject of those data (data subjects). It applies where any ‘personal data’ (as defined by the Act) are being collected, held or processed. The Act also defines a special category of personal data as ‘sensitive’ and the lawful use of these data are further restricted under the Act. See [www.legislation.gov.uk/ukpga/1998/29/contents](http://www.legislation.gov.uk/ukpga/1998/29/contents).

The Data Protection Act stipulates that personal information should not be used for the purposes of research without the approval of the individual.

## The Freedom of Information Act 2000

The Freedom of Information Act 2000<sup>5</sup> gives individuals a general right of access to information held by or on behalf of public authorities. A public authority must reply within 20 working days to any written FOIA request received from an individual to inform them whether or not the public authority holds information and, subject to exemptions, supply them with that information.

See [www.legislation.gov.uk/ukpga/2000/36/contents](http://www.legislation.gov.uk/ukpga/2000/36/contents).

More information and guidance is available from The Information Commissioner’s Office.

See [www.ico.gov.uk](http://www.ico.gov.uk).

## The Mental Capacity Act 2005/ Adults with Incapacity (Scotland) Act 2000

The Mental Capacity Act 2005<sup>6</sup> is relevant to research involving adults over the age of 16 years in England and Wales. In Scotland, the Adults with Incapacity (Scotland) Act 2000 applies<sup>16</sup>. There is no specific legislation in Northern Ireland; however, there is the common law of consent. The Mental Capacity Act does not apply to CTIMPs – the Medicines for Human Use (Clinical Trials) Regulations 2004<sup>8</sup> make legal provision for participation in CTIMPs by adults lacking the capacity to consent and the endurance of consent after the loss of capacity. See [www.legislation.gov.uk/ukpga/2005/9/contents](http://www.legislation.gov.uk/ukpga/2005/9/contents).

The Mental Capacity Act provides the legal arrangements to enable adults lacking capacity to take part in research (under certain circumstances) that would otherwise require the participant’s consent.

A helpful toolkit and other resources are available. See The Health Research Authority [www.hra.nhs.uk](http://www.hra.nhs.uk).



## The Human Tissue Act 2004

The Human Tissue Act 2004<sup>7</sup> came into force on 1 September 2006, and it is a statutory framework for dealing with issues relating to whole body donation and the removal, storage and use of human organs, tissue, and anything containing human cells, including for research purposes. Consent from the donor or nominated representative is the fundamental principle of the Human Tissue Act.

There is separate legislation in Scotland: the Human Tissue (Scotland) Act 2006<sup>17</sup>. While provisions of the Human Tissue (Scotland) Act 2006 are based on authorisation rather than consent, these are essentially both expressions of the same principle.

More information and advice is available. See:

- The HTA legislation, policies and codes of practice [www.hta.gov.uk](http://www.hta.gov.uk)
- Data and Tissues Tool Kit [www.dt-toolkit.ac.uk](http://www.dt-toolkit.ac.uk).

## Clinical Trials of Investigational Medicinal Products (CTIMPs)

The EU Clinical Trials Directive (2001/20/EC)<sup>18</sup> applies to all clinical trials evaluating the safety or efficacy of medicinal products in Europe, from 'first in man' trials to pragmatic comparisons of commonly used treatments. The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031) (as amended) transposed the directive into UK law (Figure 1).<sup>8</sup>

Authorisation by the competent authority [Medicines and Healthcare products Regulatory Agency (MHRA) in the UK] and a favourable opinion by an ethics committee is required. This authorisation is granted in the form of a clinical trial authorisation (CTA).

More information and advice is available. See:

- MHRA website [www.mhra.gov.uk](http://www.mhra.gov.uk)
- Eudralex website [http://ec.europa.eu/health/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm)
- Medical Research Council/ MHRA/Department of Health joint project on risk-proportionate approaches to the management and monitoring of clinical trials<sup>19</sup>.
- The Clinical Trials Toolkit.

## EudraCT

EudraCT is the European Clinical Trials Database used by national competent authorities to support supervision of clinical trials of investigational medicinal products. All CTIMPs with at least one site in the European Union commencing 1 May 2004 or later must be recorded in EudraCT. When recorded, a mandatory reference number (EudraCT number) is allocated and should be used in all correspondence with the MHRA, ethics committee and when reporting issues and developments such as amendments and SUSARs. Further details are available from the EMA website. See [www.ema.europa.eu/ema](http://www.ema.europa.eu/ema).

## Clinical Trials of Investigational Medicinal Products (CTIMPs) New Regulation

The EU Clinical Trials Regulation (No 536/2014) on clinical trials of medicinal products for human use, and repealing Directive 2001/20/EC will become applicable no earlier than 28 May 2016 and is likely to be in 2018. The date of applicability relates to the development and confirmation of full functionality of a new EU Portal and EU database. The date of applicability will be published in the Official Journal of the European Union. Transition periods will apply; however, organisations will be required to make changes to their processes and Trial Managers should make themselves aware of the key dates as they are made public.

## Clinical trials of Medical Devices for Human Use

Clinical trials of medical devices for human use that do not have a CE mark have specific regulations, both nationally and internationally, and must comply with The Medical Devices Regulations 2002<sup>13</sup>. In the UK, medicines and medical devices are regulated by the MHRA and detailed guidance can be found on the MHRA website. In addition to the UK regulations, internationally accepted documents and guidelines, such as ISO 14155<sup>20</sup>, should be adhered to in order to guarantee a high standard of quality.

More information and advice is available. See:

- MHRA [www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency](http://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency).
- International Organization for Standardization [www.iso.org/](http://www.iso.org/)

## IRMER Regulations

The UK Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER)<sup>21</sup> govern the exposure to ionising radiation of research volunteers. The research provisions of IRMER apply to any research exposure involving ionising radiation (i.e. it is not only concerned with exposures that are additional to routine care). When a trial involves ionising radiation, IRMER places specific responsibilities on the involved stakeholders: researchers requesting examinations; practitioners justifying and authorising individual research exposures; operators carrying out medical exposures for the purposes of research and the NHS Trust, or other responsible employer at each research site.

More information and advice is available. See:

- HRA ionising radiation resource page: [www.hra.nhs.uk/resources/before-you-apply/types-of-study/knowledgebase-ionising-radiation-2/](http://www.hra.nhs.uk/resources/before-you-apply/types-of-study/knowledgebase-ionising-radiation-2/)

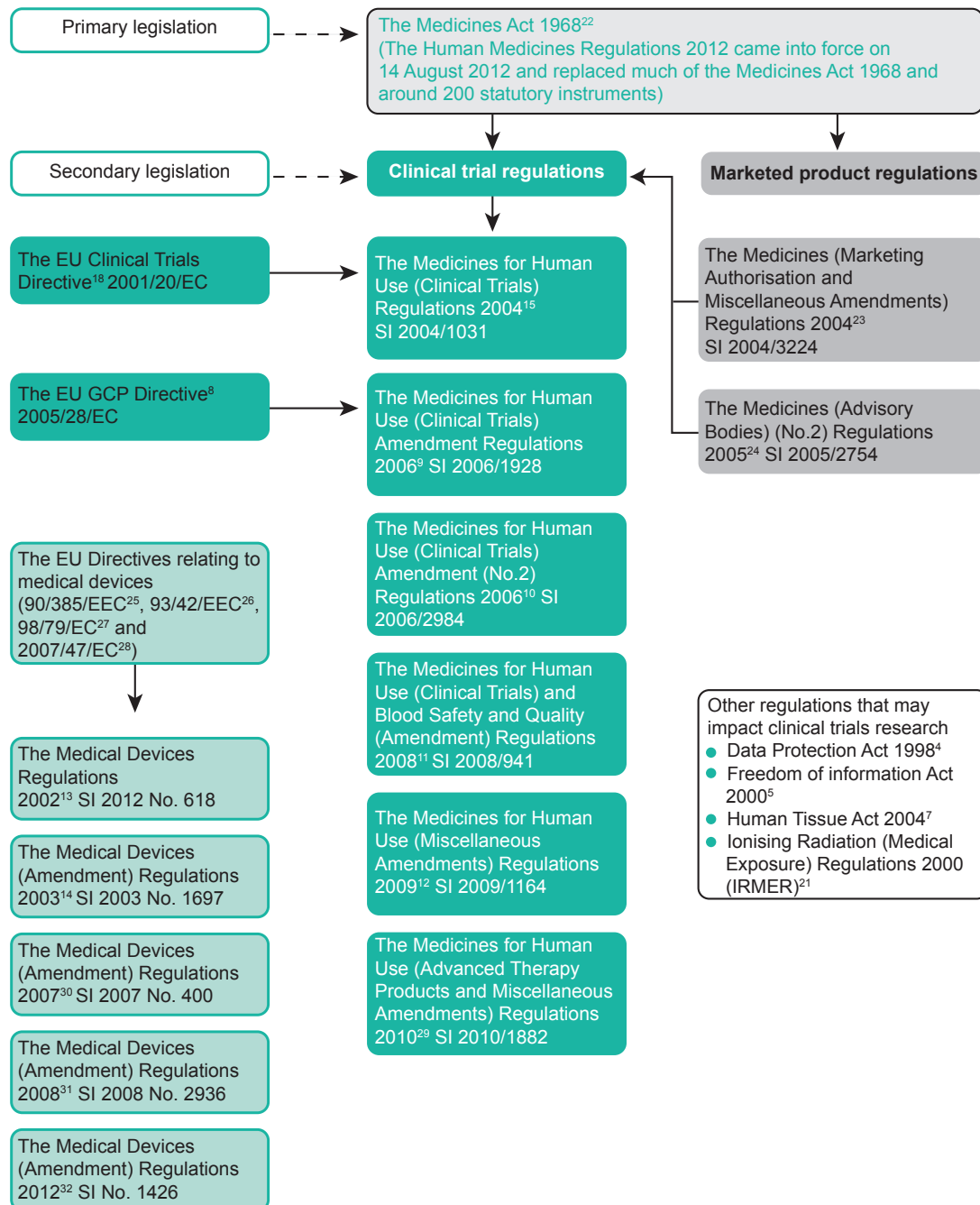


FIGURE 1 Key regulations relevant to CTIMPs and medical devices in the UK

## 3.2 Systems for approvals and permissions

All trials require approvals and permissions to be conducted; the specific requirements depend on the type of trial being undertaken (Table 2).

| Approval / Registration         | All research | CTIMP | Non CE Marked Device |
|---------------------------------|--------------|-------|----------------------|
| EudraCT                         |              | Yes   |                      |
| Research Ethics                 | Yes          | Yes   | Yes                  |
| MHRA                            |              | Yes   | Yes                  |
| Registration in public registry | Yes          | Yes   | Yes                  |
| NHS Permission                  | Yes          | Yes   | Yes                  |

Table 2 Approvals, permissions and registrations needed before a trial can commence in the UK (these steps may be done in parallel).

### Chief Investigator checklist (before seeking approvals)

This useful checklist can be obtained from the Clinical Trials Toolkit [www.ct-toolkit.ac.uk/routemap/ci-checklist-before-seeking-approval](http://www.ct-toolkit.ac.uk/routemap/ci-checklist-before-seeking-approval). The checklist has been provided to ensure all appropriate issues are considered prior to seeking approvals.

### Sponsorship

A sponsor is the organisation with overall legal responsibility for the financial management, design and conduct of a trial. 'Sponsor' does not necessarily mean the 'funder'. A funder might provide only the financial resources, although some funders may wish to take on the sponsor role.

All clinical research within the scope of the Research Governance Framework requires a sponsor(s).

For CTIMPs the sponsor has specific legal obligations which are detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004;<sup>8</sup> see the Clinical Trials Toolkit Sponsorship Station [www.ct-toolkit.ac.uk/routemap/sponsorship](http://www.ct-toolkit.ac.uk/routemap/sponsorship).

### Clinical trial registration

Trial registration refers to the publication of an internationally agreed standard dataset about a clinical trial on a publicly accessible database. The database (register) should comply with World Health Organization (WHO) standards.

It is government policy in the UK to encourage voluntary registration of trials and other well designed studies on publicly accessible registers such as ISRCTN (<http://isrctn.com>) or ClinicalTrials.gov. Clinical trial registration is not mandatory for all trials although:

- HRA has made trial registration a condition of ethical approval.
- the New Clinical Trials Regulation will make this a mandatory requirement for CTIMPs.
- the International Committee of Medical Journal Editors (ICMJE) requires that certain trials be registered on a publicly accessible database prior to the start of recruitment in order to be considered for publication in ICMJE journals see [www.icmje.org/about.html](http://www.icmje.org/about.html) and [www.icmje.org/clin\\_trial.pdf](http://www.icmje.org/clin_trial.pdf).

Registers assign unique identifiers to each trial, ensuring that the trial can be simply and unambiguously tracked throughout its life cycle from initial protocol to results publication. Registration must be complete before recruitment of the first participant to the trial.

### Ethical approval

All trials and other research studies that involve NHS participants, NHS time or NHS resources, i.e. professionals working in the NHS or NHS sites, must seek ethical approval.

All research taking place in the NHS in England requires approval for the research to commence via HRA Approval. This comprises a review by a Research Ethics Committee and an assessment of regulatory compliance, which includes where relevant a pharmacy and radiology assessment. NHS ethics approval is obtained using the centralised system called IRAS (Integrated Research Application System).

### Integrated Research Application System (IRAS)

IRAS is a single UK-wide online system for applying for the permissions and governance approvals for health and social care/community care research in the UK. It is accessible via the HRA website and captures the information needed for the approvals from the several review bodies including the Administration of Radioactive Substances Advisory Committee (ARSAC) ([www.arsac.org.uk](http://www.arsac.org.uk)) and the MHRA ([www.mhra.gov.uk](http://www.mhra.gov.uk)) amongst others.

Further information, can be accessed via the:

- IRAS guidance and a training e-module: [www.myresearchproject.org.uk/help/hlp/submissions.aspx](http://www.myresearchproject.org.uk/help/hlp/submissions.aspx).
- Health Research Authority (HRA) website [www.hra.nhs.uk/](http://www.hra.nhs.uk/).

### Gaining NHS permission for clinical research

All trials that involve NHS staff, patients, patient samples, patient records or facilities should be registered with the R&D office and require approval from the R&D directorate. A trial should be registered with R&D as early as possible in the development phase, particularly if that NHS trust is the proposed sponsor/co-sponsor.

Anyone proposing to undertake a trial must gain approval from the relevant Head of Department, for example a Head of Academic Unit, Clinical Director or Business Manager, for the facilities they intend to use. Any NHS support service requirements will be costed and reviewed as necessary.

Coordinated systems for gaining NHS permission for clinical research have been implemented across the UK.

Links to further details of the coordinating centres in England, Scotland and Wales and Northern Ireland are given below:

1. England: With the introduction of HRA approval, individual sites will be required to confirm capacity and capability according to the HRA processes.  
[www.hra.nhs.uk/research-community/the-review-process/nhs-management-permission-2/](http://www.hra.nhs.uk/research-community/the-review-process/nhs-management-permission-2/)  
[www.hra.nhs.uk/about-the-hra/our-plans-and-projects/assessment-approval/](http://www.hra.nhs.uk/about-the-hra/our-plans-and-projects/assessment-approval/).
2. Scotland: NHS Research Scotland Permissions Coordinating Centre. [www.nhsresearchscotland.org.uk/services/permissions-co-ordinating-centre/permissions](http://www.nhsresearchscotland.org.uk/services/permissions-co-ordinating-centre/permissions)
3. Wales: Health and Care Research Wales Permissions.  
[www.healthandcareresearch.gov.wales/gaining-nhs-research-permission/?force=1](http://www.healthandcareresearch.gov.wales/gaining-nhs-research-permission/?force=1).
4. Northern Ireland: Health and Social Care Application Gateway. [www.hscni.net/](http://www.hscni.net/).

In addition to the NHS R&D form, different NHS trusts/health boards may also have specific local forms that need to be completed before a trial can be approved. Contacting the relevant R&D department and talking through their R&D approval process and the time it takes for them to approve a trial is highly recommended.

### 3.3 Permissions for participant follow-up

There are several national 'registries' of patient information that can provide invaluable information for follow-up of participants, such as patient status and tracking. If you intend to access registry data, you will need approval from these agencies in addition to ethics committee approval and a CTA (if appropriate).

If you plan to use any of these services, specific details must also be included in the patient information leaflet and consent form, including a list of personal details which will be used to match data in the registry; some 'registries' will require specific wording to be included in the patient information leaflet and consent form so it is best to cross reference with the individual policy of the registry at the time. Please note that the NHS number, and in Scotland the Community Health Index number, a unique 10-digit patient identifier, should be collected to enable tracking.

## The Health and Social Care Information Centre

The Health and Social Care Information Centre (HSCIC) Data Linkage Service (DLS) incorporates the Patient Status and Tracking (PST) service and the Hospital Episode Statistics (HES) services. See Data Linkage Service provided by the HSCIC at [www.ic.nhs.uk/datalinkage](http://www.ic.nhs.uk/datalinkage).

## Patient Status and Tracking service

The PST ([www.hscic.gov.uk/dlespst/](http://www.hscic.gov.uk/dlespst/)) service is a paid-for service to support researchers in setting up and managing their research cohorts. Trial participants can be 'flagged' and the PST will report to researchers when individuals change status, for example relocate, leave the NHS, or die. This can be done as a one-off activity or repeated regularly over time.

What does patient status and tracking involve?

- A snapshot of current demographic status and mortality including cause of death where appropriate.
- Periodic long-term updates on demographic status and mortality.
- Data validation to improve linkage outcomes and/or to ensure individual records are up to date.

The cost to the researcher depends on the agreed service specification.

## Hospital Episode Statistics

Hospital Episode Statistics is the national statistical data warehouse for England of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere. HES is the data source for a wide range of health-care analysis for the NHS, government and many other organisations and individuals. For further information on the HES, see [www.hscic.gov.uk/hes](http://www.hscic.gov.uk/hes).

## Devolved Nations data linkage services

All the devolved nations have independent registries that offer medical record linkage services.

Scotland: [www.isdscotland.org](http://www.isdscotland.org)

Wales: SAIL [www.adls.ac.uk/secure-anonymised-information-linkage-databank](http://www.adls.ac.uk/secure-anonymised-information-linkage-databank)

Northern Ireland: [www.ninis2.nisra.gov.uk/](http://www.ninis2.nisra.gov.uk/)

## Section 4 Trial planning and development

The planning and development processes are closely entwined with the management of a clinical trial. It should therefore be noted that section 4 and section 5 of this Guide may have some similarities and crossover.

A clinical trial shares many features found in business projects, as defined in the field of project management. These features include:

- having a clear objective aimed to bring about change.
- effective teamwork.
- working to a set timescale.
- recognising the resources needed to achieve the objective.
- identifying tasks which need to be completed [to a pre-specified standard].

The five basic process stages of any project are:

1. Initiating
2. Planning
3. Executing
4. Monitoring and controlling
5. Analysing and reporting

Good project/trial management skills are an essential part of a Trial Manager's role. There are numerous online project management resources available including MS Project and other similar software. These comprise tools for: developing project plans and timelines; evaluating risk and planning contingency; establishing clear processes; coordinating resources including staff; monitoring progress and quality assurance.

In order to deliver a clinical trial successfully, the following points should be observed:

- **Scope/quality:** this includes ensuring that the requisite number of participants are recruited and that recorded data is of high quality. This is usually the highest priority for a non-commercial trial and needs careful initial planning and subsequent management.
- **Budget:** risks to the budget should be minimised during the planning stage and forecasting carried out at regular intervals throughout the trial. Funding supplements are both time consuming and difficult to justify and so should be avoided wherever possible.
- **Timelines:** it is essential that realistic timelines are planned initially and reviewed regularly during the trial. It may sometimes be necessary to extend trial timelines, for example as a result of delays to approvals or slow recruitment of participants. Timeline-only extensions can be requested but must be fully justified and requested early. For a commercial trial, timelines may be a higher priority than budget.

In addition, the following principles contribute to the successful delivery of a trial:

- Identifying and mitigating risks (see Section 4.3). All risks to the trial should be rated in terms of likelihood of occurrence and impact:
  - ➔ Major risks (high likelihood and high impact) should be reduced or avoided by re-planning
  - ➔ Medium risks (high likelihood or high impact) should have mitigating strategies put in place
  - ➔ Minor risks (low likelihood and low impact) should be documented
- Maintaining good communication with all relevant parties.
- Determining the work required and developing a schedule with milestones, i.e. identifying what needs to be achieved and when. The critical path is the schedule of work that determines the duration of the trial which, if delayed, can affect the entire trial. This should be the prime focus of attention during the management of the trial and assisted with use of a Gantt chart.
- Determining the resources required during the stages of the trial and the associated budget schedule.



- Monitoring quality, timelines, budget and resources in comparison with the trial and budget schedules, determining the cause and impact of any variance and taking corrective action where required. Changes in scope, for example, adding extra sites or increasing recruitment targets also need to be managed carefully and the impact on the trial needs to be analysed.
- Managing the trial efficiently by disseminating appropriate information to all those involved in the trial, ensuring that everyone is aware of their role and the relevant issues.

## 4.1 Planning a grant application for a trial

The starting point for any trial is the research idea, and a grant or funding application normally follows. There are several places to obtain advice and support for developing trial grant applications.

### Trial design support

The NIHR Research Design Service (RDS) (see NIHR RDS map: [www.rds.nihr.ac.uk](http://www.rds.nihr.ac.uk)) in England provides design and methodology help for researchers to prepare funding applications for submission to NIHR and other national, peer-reviewed competitions for applied health or social care research.

It is recommended that Chief Investigators (CIs) approach a Clinical Trials Unit (CTU) which has expertise in coordinating trials, trial design, trial management, data management and analysis. Some funders expect a trial application to be developed in partnership with a suitably qualified unit. Early engagement with a CTU providing support is very important. Information on the UKCRC-registered CTUs can be found via the UKCRC registered CTUs' Resource Finder at [www.ukcrc-ctu.org.uk](http://www.ukcrc-ctu.org.uk).

### Preparing the grant application

The grant application is usually developed by a multidisciplinary team, comprising clinical input related to the research as well as methodological, trial design and trial conduct expertise. Typically, the Chief Investigator will be the lead applicant, supported by co-applicants relevant to the expertise required; for example, a health economist would be relevant for a trial with cost-effectiveness outcomes. All trials require statistical advice for trial design, statistical design, sample size calculations and analysis planning. Inclusion of a Trial Manager at the planning stage can also help to highlight operational, ethical and regulatory issues to be addressed in the trial. It is also important to consider a patient/participant perspective.

Applications to most funding schemes typically require an initial brief 'outline' or expression of interest. If successful, a more detailed 'full' application will follow. The full application is similar to a brief protocol, and should include, for example, information about trial background, design, statistical considerations, data collection and team expertise. In addition, applications will need to include details of co-applicants' CVs and costs; it should be borne in mind that this process can take considerable time and the days before the submission deadline can be stressful.

Most funders have online application forms but they usually also require a formal 'sign-off' by the CI, the head of department or institution, the administrative authority (typically a university or NHS trust where staff, facilities or patients are based) as well as financial approval by the host institution.

### Resource requirements for a grant application

The resources required to conduct the trial need to be identified at the grant application stage. Trials funded through the NIHR, Medical Research Council (MRC), members of the Association of Medical Research Charities (AMRC) and most other funders will comprise three cost types:

- Research Costs: costs attributed to the funder body for 'conducting' the research.
- Service Support Costs: met from R&D budgets of the health departments of the UK; in England this is often via the CRN. Such costs include the participant care costs, which would end once research completes, even if the treatment / intervention continues, for example, appointments to obtain consent or in-patient stays for research purposes.

- Treatment Costs: covered by NHS commissioning arrangements. These include care costs that would be ongoing if the treatment / intervention continued in 'real care', for example: drug/intervention costs, (including administration and infusion time) and therapist time. The difference between standard treatment and the experimental treatment cost is referred to as the 'Excess Treatment Cost' (ETC). In calculating ETCs, the intervention is assumed to be successful and adopted into routine care. If ETCs are substantial, subvention funding may be available from the Department of Health ([www.dh.gov.uk](http://www.dh.gov.uk)).

In England, industry-funded but academically led/sponsored trials are not eligible to receive support costs or treatment costs without adoption onto the NIHR portfolio. Industry-sponsored studies operate at full cost recovery. More detailed information can be found in funders' guidelines.

Further information about these different costs is given in the Department of Health's document:

Attributing the costs of health and social care research and development (AcoRD) ([www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance)).

The AcoRD guidance must be used to attribute the cost of research taking place in the NHS where the outline of full grant funding application was submitted to funders after 1 October 2012.

### Costing a research grant

Consulting both the specific funder guidance and that of the host organisation will provide information on the costs which can or cannot be included in the grant. For larger multicentre trials, typically the host will be a university or NHS trust and, as such, the host will hold the budget. Universities use a full economic costing (FEC) model, which the host organisation's research development staff will advise on.

One way to establish research costs is to determine the time required for each of the main phases of the trial: set-up, recruitment and follow-up and analysis. The staffing structure will vary but may typically include staff for trial and data management, clerical and data entry support, statistics and database programming. Trial size and complexity as well as the amount and type of data to be collected will influence staffing. The trial risk assessment, monitoring and management plans should form part of the grant application. Risk assessment at this planning stage may identify additional needs during the trial, for example: extra monitoring visits, increased staffing levels and/or more frequent DMC reviews. In summary, identify all the main trial tasks, establish responsibility for carrying them out and estimate the length of time each task will take to complete. University staff may have access to Sirius web ([www.siriusweb.leeds.ac.uk/offerSub.asp](http://www.siriusweb.leeds.ac.uk/offerSub.asp)) or a similar calculator to assess costs for you. Within the NHS, the R&D department can provide similar support.

### Trial/research budget checklist

- Salaries for trial staff including (but not limited to) statisticians, health economists, qualitative researchers, the trial team.
- IMP/intervention/device costs including: drug/placebo manufacture, labelling, blinding, device or intervention purchase, testing, shipping and destruction.
- Equipment purchase, testing and delivery e.g. centrifuges, freezers, monitors, etc.
- MHRA fees (CTIMP only).
- Laboratory or other test fees.
- 'Flagging' of participant records if required for long-term trial follow-up with Health and Social Care Information Centre ([www.hscic.gov.uk](http://www.hscic.gov.uk)).
- Randomisation system development or purchase.
- Database design/data collection system, development or purchase.
- Computing: hardware, software, computer consumables.
- Web design costs.
- Printing and postage costs: protocols, consent forms, data forms, questionnaires, posters and newsletters, questionnaires, Freepost licence (for participants to return questionnaires). Note: allow for postage cost increases over time and multiple mailings for non-responders. Utilise web distribution for newsletters and/or newsletters to reduce costs where possible.
- Consumables: stationery, office furniture, filing cabinets, photocopying.
- Participant expenses and incentives: small gifts, pens or gift vouchers and participant travel expenses (subject to funder approval).
- Public involvement: travel expenses, out-of-pocket expenses and payment for involvement.

- Telephone/fax/email: to maintain regular contact with sites and participants, include text messages if appropriate.
- Advertising costs if used to aid recruitment.
- Site costs: telephones, internet, photocopying, fax, data collection, nursing support staff and other site staff.
- Travel for site visits for initiation, training, monitoring and close-out meetings. Also include researcher costs, possibly including accommodation and subsistence.
- Meetings: trial management, steering and monitoring groups and other meetings. Additional costs may include room hire, travel and refreshments. Consider opportunities to reduce the trial carbon footprint and reduce costs, e.g. teleconferencing / online meeting facilities.
- Publication and dissemination: protocol publication costs, mail shots to participants (including postage costs), journal publication fees which may include Open Access fees and attendance at conferences.
- Archiving and storage: sufficient resources will be needed to allow archiving according to the appropriate regulations (see Section 9).

To plan specific service support and treatment costs, compile a visit schedule and outline the tests or activities which will occur at each point. This is likely to include screening and randomisation as well as treatment and tests (determining the number and purpose of tests). Establish whether the associated costs should be categorised as service support, treatment or research. It is important to discuss service support costs with the CRN early in trial development; similarly, for treatment costs, liaise with the appropriate NHS trust's R&D department and the sponsor.

If the grant application is successful, funding is usually released upon contract signature or an agreed date post signature. This may be some months after receiving the initial award letter. Financial accounts and budgets will need to be set up within the relevant host organisation and are normally activated upon staff appointments, but most organisations will require confirmation of funding prior to approving new appointments and committing to expenditure.

## 4.2 Public involvement

Involving the public in your trial can help to improve the quality, relevance and acceptability of the trial to potential trial participants. This section has been written with the assistance of INVOLVE which is a national advisory body funded by the NIHR to support public involvement in NHS, public health and social care research ([www.involve.nihr.ac.uk](http://www.involve.nihr.ac.uk)).

INVOLVE defines public involvement in research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. This includes, for example, offering advice as members of a project steering group and commenting on and developing research materials. Public involvement is different from people being involved as participants in trials. The following are some of the ways that public involvement can help.

Improving the quality and acceptability of the trial by:

- making the language and content of information provided more appropriate and accessible.
- helping to ensure that the methods proposed are acceptable and sensitive to the situations of potential participants.
- helping to ensure that the trial uses outcomes that are important and relevant to the public.
- increasing participation in research, as a result of making the research design appropriate and acceptable to participants and improving the information provided so that participants can make informed choices.

Making the research more relevant by:

- potentially identifying a wider set of research topics than if health professionals had worked alone.
- ensuring that research is focused on the public's interests and concerns, and that money and resources are used efficiently.
- helping to reshape and clarify the research.

It should be noted that, unlike recruiting participants into trials, involving people in trials in a research advisory, consultative or collaborative capacity does not require specific ethical approval. [www.invo.org.uk/posttypepublication/patient-and-public-involvement-in-research-and-research-ethics-committee-review/](http://www.invo.org.uk/posttypepublication/patient-and-public-involvement-in-research-and-research-ethics-committee-review/).

To help plan public involvement in a trial, INVOLVE suggests consideration of the following points:

- Be flexible in your approach. For good reasons, trials are managed in quite a rigid way. However, if you want to make these processes accessible to members of the public, patients and carers, then a degree of flexibility is needed. There is a balance to be had. This may mean being open to running meetings in a different way.
- Don't be too prescriptive about what you want people to do – otherwise there is a risk that you will always get the same people coming forward who fit that role. Perhaps, try an asset-based approach – take some time to identify the skills and experiences of the people you are working with and build on what they already bring to the table.
- Consider when to involve people. In general, this should be as early as possible in the development and design of your trial; for example, consider involvement in grant applications or in developing the protocol. One way to ensure this is by involvement across a programme of research, or at a departmental level.
- The people selected may be involved in the trial over a long period of time and so the working relationship between researchers and members of the public is very important. Therefore, think about different options for recruitment. Is a 'formal' interview the best approach – is it likely to identify the best people for the role, or would a different method be more appropriate? See INVOLVE briefing note six: 'Who should I involve and how do I find people?' [www.invo.org.uk/resource-centre/resource-for-researchers](http://www.invo.org.uk/resource-centre/resource-for-researchers).
- Develop terms of reference and role descriptions for members of the public and try to establish ways of working that suit all members of the team from the beginning.
- Be honest about what aspects of the trial design can and cannot be changed, and clearly explain the reasons for this. You should try to be open to new suggestions and to doing things in new ways when possible and appropriate.
- Think about designating a mentor – perhaps a member of the research team – who people know they can approach with questions about the trial, for clarification about the process, or who can provide support as required. Over a programme of research, more experienced patients may be able to take on a mentoring role with newer members of the public.
- Trials are complicated so people need to be well supported.
- Think about people's personal development. It is important to consider what the people involved in the research are getting from the experience as well as the impact on the research. Developing people will also benefit future trials that they are involved in.
- Establishing and maintaining good communications is vital for successful involvement, and bear in mind the advice about flexibility. Some people prefer phone calls, some like emails. Some will be comfortable with teleconferencing, but for others this may be a difficult and ineffective way for them to contribute.
- Plan to provide feedback to the people you involve to let them know how their contribution has helped – or be able to explain where you haven't been able to take their views on board. People often feel they are consulted, without seeing any change as a result.

More information, guidance and practical tips are available from the 'Resources for Researchers' section of the INVOLVE website ([www.invo.org.uk/resource-centre/resource-for-researchers/](http://www.invo.org.uk/resource-centre/resource-for-researchers/)).

### 4.3 Risk assessment

The purpose of risk assessment is to identify the potential risks associated with the trial, to assess the likelihood of those risks occurring and resulting in harm to participants, trial failure and damage to institutional reputation. This assessment should inform the development of relevant risk-mitigation plans along with proportionate trial management and monitoring plans.

The first high-level risk assessment should be undertaken prior to submission of a funding application so that appropriate operational resource requirements are considered and requested. A more detailed assessment is then undertaken at an early stage in the development of the protocol.

The risk assessment may be led by the Sponsor/Chief Investigator/Trial Manager or protocol author but should include input from all the members of the trial team. It may also be reviewed by other key stakeholders, such as the funder and other investigators, to facilitate agreement on the main risks inherent

in the trial protocol.

The risk assessment would normally include:<sup>19</sup>

- the risks to participant safety in relation to the intervention and clinical procedures.
- the risks to participant rights.
- all other risks related to the design and methods of the trial, including risks to reliability of results.

The risk assessment and associated plans should be documented so that the management strategy is both transparent and justified. It can also form the basis of a common understanding by all stakeholders on the risks for the trial. This documentation, which may be included in the protocol or in trial-specific procedures and plans, will not only facilitate the management of the trial but can be used in the course of an audit or regulatory inspection to justify the approaches taken.

For CTIMP trials, the IMP risk category and safety-monitoring plan may be submitted to the MHRA with the Clinical Trial Authorisation (CTA) to ensure that there is shared understanding on this key aspect of the trial.

Active sponsor and trial team oversight and regular reviews of the risk assessment during the course of the trial are essential in any risk-adapted model. This will ensure that there is escalation/moderation of activity in response to incoming data and feedback on trial progress and conduct.

#### 4.4 The trial protocol

The trial protocol is the document that describes the scientific idea, the hypothesis to be evaluated and the operational procedures, so must be clear, unambiguous and understandable. The protocol will be read by many different stakeholders: funders, investigators, collaborators, internal and external reviewers, regulatory bodies and participants. Potentially this will also be published on the web or in a journal. The Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines can assist in standardising protocols ([www.spirit-statement.org](http://www.spirit-statement.org)), with checklists and publications available. The Health Research Authority also has templates available for use ([www.hra.nhs.uk/](http://www.hra.nhs.uk/)) which follow the SPIRIT guidelines.

It is important to note that the trial sponsor may also have protocol guidelines and templates which you may need to follow.

#### Key points for a protocol

- It has to be clear and concise, accurate and thorough.
- It is the critical document to get right – a poorly written protocol can highlight a potentially poorly designed trial.
- Errors, omissions and inaccurate or unclear writing can have a significant impact on trial recruitment and conduct.
- Consider the structure and basic components – a good place to start is the contents' page.
- A protocol for a CTIMP may be very different in size and scale to a small observational study – it has to be appropriate and proportionate.
- Ensure that it has a structure that is logical and flows, and that items follow through the different sections. This is particularly important when making amendments: cross-check the implications of every change throughout the document.
- Protocols tend to be lengthy, complex documents. Proofreading by others is key.
- Public involvement in the design of the protocol can help in assessing potential feasibility and acceptability to participants.
- Consistency in terminology, phrases and procedures is crucial; consider creating and using a style guide. A glossary can also be useful.
- Evidence of clinical equipoise is important – strong opinions about a particular treatment can be unhelpful.
- Every protocol will need amendments but, as the number increases, so does the workload and the goodwill of sites may decrease. As a result it is advisable to ensure that your protocol is fit for purpose from the start.

#### Writing a trial protocol

- There should be one individual with editorial control and oversight of the writing process. This person



can also coordinate sections created by others, for example a statistical plan.

- Appoint a protocol writing group – a protocol needs input from many different people and this process needs careful management.
- Do not reinvent the wheel – if you have a similar research project with a good protocol, use that as a template. Many sponsors have protocol templates which you may be required to use.
- Peer review of the protocol will ensure it is fit for purpose.
- Implement strict version control and an archiving policy.
- Writing a protocol will take longer than you anticipate. Plan carefully and devise a realistic timeline.

### Protocol and trial publications policy

The publication and presentation policy should be agreed at the start of the trial by the Trial Steering Committee (TSC) and should ideally form part of the protocol. The publication policy will define arrangements for authorship. Large trials may have group authorship, with a list of contributors giving details of who did what, for example: Trial Steering Committee, collaborating investigators and acknowledging participants.

One of the first publications from the trial may be the trial protocol. The protocol should be submitted, ideally, at the start of the trial but protocols will be accepted up to the end of participant recruitment, for example to Trials journal.

No publications or presentations with trial outcomes should be produced before the primary paper has been agreed and accepted for publication, without the prior approval of the TSC. It is, however, often possible to publish baseline or substudy papers prior to the main trial publications. It should be noted that many funders will require notification (and possibly approval) of any publications arising from their funding.

### 4.5 Randomisation options

The randomisation process must be designed in the planning stage and must ensure:

- that participant details are recorded prior to intervention allocation.
- that adequate concealment is achieved and investigators and trial staff are not able to access or predict the next intervention allocation.

Investigate whether or not telephone or web randomisation will be possible from sites, i.e. is there access to these technologies in the clinical areas where participants will be present?

**External systems** include central telephone randomisation, web-based systems, email or fax to the coordinating centre and automated electronic systems with voice-mail recognition. An automated electronic system with voice-recognition or a web-based system is the optimal method of randomisation as it is set up by independent operators and captures baseline details as soon as the participant is entered into the trial so they can be tracked for outcome data. The treatment allocation is held electronically and is secure.

**Internal systems** may include allocation codes held by pharmacy, randomisation envelopes, or sequentially numbered intervention packs. These systems are less secure as it may be possible to subvert the allocation if an investigator wants a particular allocation for a participant. There is no central record that the allocation has been taken and abandoned without the site being monitored regularly or intensive cross-checking of allocations.

### 4.6 Trial oversight

Arrangements for the oversight of trials will vary according to the nature of the trial and should be proportionate to the complexity and associated risks. Different funders may also have particular requirements. Trial managers should always work to the specific requirements of the funder and sponsor. Commonly, trials are overseen by three committees: the Trial Management Group (TMG), the Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC). The arrangements for trial oversight should be detailed in the protocol.



## Trial Management Group

The TMG oversees the day-to-day management and overall conduct and progress of the trial. The group normally includes the Chief Investigator, a trial manager, a statistician etc. In addition, the group may include other members of the trial team with specific expertise, such as the Database Programmer, Pharmacist, Health Economist and one or two site Principal Investigators.

Group meetings are essential to keep members up to date with the trial and to monitor progress.

The frequency of meetings is trial dependent; however, it is recommended that this group would meet frequently during trial set-up and at least quarterly thereafter. A meeting should also be held before a TSC meeting to plan the agenda and required meeting papers.

## Trial Steering Committee

The role of the TSC is to provide independent oversight of the trial on behalf of the sponsor and funder, and to ensure that the trial is conducted in accordance with the principles of GCP and relevant regulations. The TSC should focus on the progress of the trial, adherence to the protocol and participant safety. In addition, the TSC should review any relevant emerging information regarding the intervention or clinical procedure that may have an impact on the trial. The terms of reference should be agreed at the start of the first meeting of the committee.

It is recommended that a TSC includes an independent chair, has a majority of independent voting members and includes a public/patient representative. The non-independent members would normally include the Chief Investigator and one or two other investigators. Representatives from the sponsor and funder may be invited to meetings. Relevant members of the TMG should attend committee meetings to present information as required.

## Data Monitoring Committee

The role of the DMC is to monitor accumulating data from the trial at pre-specified intervals, in particular in relation to safety and efficacy, and make recommendations to the TSC regarding any safety issues that should be brought to the attention of investigators or any ethical reasons why the trial should not continue. Usually the DMC is the only group to have access to unblinded data during the course of the trial. In addition, it considers whether or not any interim analyses are required and would review these data. All members should be totally independent of the trial. The DMC is usually made up of three or four members and includes an independent chair and experts in the field such as clinicians with expertise in the relevant area and expert statisticians. Trial statisticians usually attend meetings and present the data. The Chair will report his or her recommendations to the Chair of the TSC.

The DMC terms of reference, or charter, should be agreed before the start of the trial. This document will outline any stopping rules and the frequency of interim data analyses during the recruitment phase of the trial. Recommendations for the content of a DMC charter can be found at [www.abdn.ac.uk/hsru/documents/damocles2](http://www.abdn.ac.uk/hsru/documents/damocles2).

It is expected that nearly all RCTs will have a DMC; however, for relatively small and/or low risk trials, the TSC may also assume this role. The TSC or the funder and/or sponsor may decide this.

Meetings are usually held annually; however, the DMC can meet more frequently if necessary. Meetings should be scheduled prior to the date of the TSC meetings to allow enough time for the Chair of the DMC to report to the Chair of the TSC.

## 4.7 Regular reporting

It is very important to consider what reports will be required, who you have to report to and when. This will ensure that reporting milestones are met. Funding bodies have rules for what needs to be reported, including some outputs or where they need to be informed of activities, for example, NIHR HTA consider participants' materials to be outputs, see [www.nets.nihr.ac.uk/\\_\\_data/assets/pdf\\_file/0008/35972/Guidanceonoutputs.pdf](http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0008/35972/Guidanceonoutputs.pdf).

The project plan should include the deadline dates for all scheduled reports. There are several questions that you should consider to inform the reporting plan:

### **Which bodies need a report?**

These are very likely to include the REC, the sponsor(s), the funder, trial-specific committees, NHS R&D and, depending on the type of trial, the MHRA.

### **What types of reports are required?**

The type of report depends on the type of trial and the body you are required to report to. It is likely to include progress reports, safety reports or Development Safety Update Reports (DSURs), recruitment data, and an end-of-trial report.

### **Who will produce reports?**

This will vary depending on the type of report but could include the Chief Investigator, trial manager, statistician, IT team or several team members.

### **How often are reports required and in what format?**

Be aware of the timing and frequency for each type of report.

Check format required for submission, for example electronic or paper.

### **What data are required to be included in the report?**

For example, recruitment data, safety data, blinded or unblinded data.

### **Financial reporting:**

Consider when, what and to whom you need to report the status of the trial finances. Regular reports to the Chief Investigator during TMG meetings will be necessary as well as, possibly, an annual report to the TSC and the funder.

Funders will have their own report to be completed at set time points. Annual reconciliations may also be compiled by the host finance department.

### **The CTU is responsible for a portfolio of trials:**

Where possible sequence meetings, especially DMC, so that the reports are not all due at the same time.

## Section 5 Trial set-up

As noted in section 4 there can be a lot of overlap between the planning and the set-up of a trial; these are not mutually exclusive processes and may run in parallel.

Trial set-up is the phase where the protocol becomes operationalised. The set-up phase can take many months and the workload should never be under-estimated so the estimated start date for the trial should be realistic. This is a very busy and complex stage of a trial as there are many issues to consider and several steps to undertake. At this stage the essential elements required before a trial can start must be considered, actioned and then finalised.

### 5.1 Trial coordinating centre

#### What is a trial coordinating centre?

The trial coordinating centre is at the heart of the trial, whether it is a single-site or multicentre trial. It can be referred to by a variety of names and set in many different environments. It can be:

- part of a dedicated CTU.
- an office/desk in a clinical department in a hospital or GP practice.
- an office/desk in an academic department in a university.

#### The coordinating centre will need:

- contracts or agreements with: the funder, the sponsor and the host institution (which may also be the sponsor) which will determine delegated tasks, space, staff and equipment.
- systems for data management, administration, finance and personnel management.

Remember the trial will grow – data requires a lot of space, and additional staff may be required as the trial progresses.

A typical coordinating centre trial team consists of the following:

- Chief Investigator(s)
- Trial Manager
- Administrative support
- Programmer/IT support
- Database Manager and/or Data Assistant
- Statistician
- Pharmacy support (CTIMP)

The trial team is determined by the needs of the trial and could change over the course of the trial. The trial may need more of one skill and less of another, for example two data assistants and 0.5 of a programmer. Begin to incorporate the functions, responsibilities, competencies required and likely workload hot spots as part of the project management plan.

### 5.2 The trial team

The following team members are not set in stone; different institutions and organisations will have varying titles and roles for the members of what they may term a “typical” trial team. The Chief Investigator title/role, however, will remain the same.

#### Chief Investigator

The Chief Investigator (CI) is the person who has developed, with the co-applicants, the trial, design and methodology, and applied for funding. The Chief Investigator is an expert in the field. The CI should be committed and supportive, and should value the trial team. A good relationship between the Chief Investigator and Trial Manager is vital; these two people usually take overall responsibility for the management of the trial. While the CI takes overall responsibility for the whole trial, they do not have to be involved in the day-to-day management.

## Trial Manager

Excellent trial management is the key to successful trial delivery. The Trial Manager coordinates and is responsible for the day to day activities of a trial and therefore holds a pivotal position. Successful trial managers need to be multitasking, hard-working, well organised with an ability to multi-task, capable planners and excellent communicators. Never underestimate the importance of common sense and attention to detail. Further details of the competencies required to be a trial manager can be found at [www.tmn.ac.uk](http://www.tmn.ac.uk).

## Administrative support

This is a key support role with varying responsibilities and title. This can range from: administrator, clinical trial administrator (CTA), data officer or trial secretary. The role, as you will see from the titles, can vary greatly and may be combined with the data assistant role (see below) often dependent on the specific needs of the trial. The person in this administrative role will work closely with the Trial Manager and may support the whole trial team. This person should have IT and organisational skills, with good communication skills and attention to detail. It should be noted that not every trial will have this level of support.

## Programmer

The Programmer will develop computer programs for trial data management, trial administration, analyses and for general trial monitoring systems. If commercial software is used, less programming/IT support may be required but it will still need to be validated against the specific trial needs. The Programmer will work closely with the Trial Manager and Statistician as knowledge of RCTs in general and in particular an in-depth knowledge of the trial being conducted will be essential. The Programmer will be needed throughout the trial to develop, establish and maintain the programs.

## Data Manager

The Data Manager will ensure that all necessary data is collected in a timely manner by working closely with the Programmer and Trial Manager to ensure that the database design will allow for the necessary prompts and reports to facilitate timely data collection. The Data Manager should have substantial involvement in the trial from the planning stage and will have an in depth knowledge of the trial's data collection and management systems.

## Data Assistant

The Data Assistant's role combines data processing with many other office duties, for example, filing and mail-shots. This is a crucial role as accurate and complete data is essential.

## Statistician

The role of the Statistician is to ensure that the sample size estimation is accurate and that the interim and final analyses mirror the outcomes in the protocol and that the analyses are conducted according to a Statistical Analysis Plan. Therefore, a trial will rarely need full-time statistical support as their input is concentrated around the planning phase, monitoring data quality, interim and final analyses. This aspect of a trial could be provided by someone outside the coordinating centre, for example, in an expert unit. It is essential that the Statistician is committed and involved from the start of the trial to ensure that the data required will be collected.

Remember: not all trials will need a team as described above. There may also be other team members, for example, health economists, social scientists and qualitative researchers, as appropriate to the trial. Roles may be combined or on a part-time basis or seconded from elsewhere, including the host institution.

## 5.3 Trial identity and marketing/the trial as a business

Consider treating the trial as a business by adopting methodologies and management techniques from the business world. Francis et al.<sup>33</sup> suggested that dimensions of running a successful trial include 'marketing', 'sales' and 'on-going client management', and developed a reference model from marketing theory.

Serious thought should be given to how the trial will reach the widest relevant audience and be inclusive. The trial needs to be promoted both to ensure that it is at the forefront of investigators' minds and also to engage with participants. Promotion and marketing of the trial are important components of the overall trial management plan.

### Consider the following:

- Aim to give the trial an individual identity.
- The name, acronym and logo should be recognisable and memorable.
- Consult the relevant experts and make use of medical illustrations, departmental reprographics, etc. as this can help provide a professional appearance.
- Promote the trial identity – make it known – always use it and publicise it.
- Produce a marketing plan.
- Use social media to promote the trial and provide progress updates. Check who needs to know what and where you're posting information e.g. ethics and host institution.
- Use the trial identity on all customised stationery, data forms and other promotional materials.
- Set up dedicated telephone lines, answering machines, fax machines, email addresses and website addresses.

The sponsor may need to approve any trial identity logos, etc. to ensure there is no conflict with their corporate identity.

## 5.4 Standard Operating Procedures

Standard Operating Procedures (SOPs) should be developed for all aspects of trial conduct and management in order to ensure that trials are conducted and data generated, recorded and reported in compliance with the protocol, the principles of GCP and applicable regulatory requirements. SOPs should comprise detailed, clear and concise written instructions designed to ensure that performance of an activity is standard, regardless of who is carrying it out. The trial sponsor will usually expect their own SOPs to be followed, unless specified in the contracts. A number of organisations also provide example SOPs on their websites and many CTUs have core SOPs.

### Topics covered include:

- Protocol content and format.
- Risk assessment.
- Document version control.
- Setting up and maintaining a Trial Master File (TMF).
- Design and development of Case Record/Report Forms (CRFs).
- Database design.
- Managing and reporting adverse events.
- Monitoring and source data verification.
- Drug pack (intervention) management systems if needed.
- Statistical analysis plan.
- Reporting.
- Archiving of essential documents.

The trial team must follow the designated SOPs but would not, in general, be required to write them. However, Trial-Specific Operating Procedures (TSOPs) must be developed for each trial. These may also be referred to as MOPs (Manual of Operations or Modified Operating Procedures) and provide guidance on how more general SOPs would be followed by the team in the trial specified. Examples include:

- Reporting pathways for adverse events.
- Monitoring and management plans.

## 5.5 Document development and design

Multiple documents are required to successfully conduct a clinical trial and time should be allowed to ensure that all documents are fit for purpose. The items included are not only essential documents such as the protocol, participant information and informed consent form, to name a few, but also many other documents which are needed to effectively manage a trial. These include: planning documents such as the monitoring plan and risk assessment, also independent oversight details (TSC and DMEC where needed).

The sponsor or host institution will usually have templates for core trial documents (and indeed may mandate their use) so don't reinvent the wheel at the start of each trial.

Additionally, to ensure that people will understand clearly what the trial is about and what it entails, all documentation should be written in a clear, unambiguous way. Scientific terms and jargon are unlikely to be understood by participants and must be used only when necessary and clearly explained.

### Some general tips

- Think about the reader as a person – use 'you'.
- Be reader-centric.
- Use appropriate language and avoid jargon.
- Keep it short and simple.
- Cut out unnecessary words and phrases.
- Pilot your information appropriately for the planned participant group and revise using the feedback obtained.
- Think about relevance to the audience or specific requirements, for example, shortened versions for use in emergency situations, large print for those with sight issues or the elderly.
- Consider other communication styles such as audio recording, simple language and pictures for young children.

**Note: PPI involvement at this stage is very important.**

## 5.6 Trial information systems

Trials have a number of information system requirements; all will need a robust platform for entering and managing data. Most will also require a facility to run reports and a mechanism to extract data for analysis. Some trials might also require more specific systems, for example, to manage automated mail-out of appointment letters or importation of laboratory results.

All computer systems require validation; that is, it can be demonstrated that a system is working reliably and as specified. Validation is regarded as both good practice and an essential regulatory requirement. Costing staff time to develop a computerised trial system, carry out essential validation testing and maintaining it for the lifetime of the trial must be part of the overall trial costs and considered during the application planning stage.

A key strategic decision is whether to build systems in-house or to purchase an existing commercial system, for example, Inform, MACRO Electronic Data Capture (InferMed, London, UK), Rave (Medidata, New York, NY, USA), OpenClinica (Waltham, MA, USA).

### System design

Each system needs a specification, i.e. a document describing the objective of the system and listing each functional component. The specification guides implementation and facilitates the testing procedure. Each version of a system is assigned a number to link documentation to the development, test and live systems. The test version can be used not only for development but also to train new users on the system.

The key component of the system is the data entry and management tool, often referred to as the 'trial database'. The following rules should be observed when creating this tool:

- Computer screen design should be kept as simple as possible. Designing the screen to match the paper data collection forms will greatly enhance the quality of data input.
- Minimise the number of different screens needed – to avoid excessive scrolling, use tabs to move from one related section to another.
- Minimise the number of times you need to hit 'Enter' and have options to 'Save', 'Save and Continue' or 'Cancel'. Put these as action buttons at the top and bottom of each screen to minimise the need for scrolling up and down.
- Context-sensitive 'Help' text where necessary – a box with a '?' is standard for this.
- Put units of measurement next to the input field so users need to enter only the actual number – this can be useful in international trials where different countries may use different units.
- Drop-down lists for multiple-choice answers need less screen space than listing every choice and restricting the user to inputting only valid responses.
- Drop-down options or encoded answers should use standard conventions throughout.



- Data checks can be applied to show warnings should an out-of-range value be entered.
- Further constraints can sometimes be added to enable/disable specific electronic CRFs (eCRFs).

Never underestimate the time required for user testing prior to finalising the database. This is time well spent!

eCRFs are made available over the internet, allowing site staff to enter data directly. The majority of commercial packaged solutions provide a data entry system and a database. If you require the system to perform extra administrative or trial management tasks then you will need to do these manually or on a different system.

If you have a bespoke system created this can include a lot of extra functionality such as standard reports. This can save a great deal of clerical and management time and associated costs. Data is stored in a back-end database, commonly Microsoft SQL Server, Oracle or MySQL. A well-designed database needs a degree of expertise to design and this should be a joint effort with the Database Designer and the Trial Manager. Ensure that all data are collected and stored only once within the database. Ensure that the database holds descriptors of the fields used and any coded values. These will be used to create a data dictionary that will describe any exported data used for analysis.

As discussed in Section 4.5, the randomisation system must be integrated into the trial IT system design. This should be discussed with the Programmer, Database Designer or IT team.

A security policy governing all aspects of data collection, data management, analysis and archiving is essential. It is essential that all data (where applicable) are collected, used and stored within the confines of the Data Protection Act 1998. It is important to discuss this with the IT department in the sponsor/host organisation as high level organisational security policies will exist.

All users must be given a unique username and password to gain access to the database and be required to give a written assurance not to share this with anyone else. Individual users are assigned roles such as data entry, data view only, which limits activity and access to specific trials. A full audit trail is essential. Security and audit are seen by regulators as key requirements.

A detailed discussion of data and system standards can be found in the UKCRC Data and Information Management Systems (DIMS) Project. See <http://www.ukcrc.org/research-infrastructure/clinical-trials-units/data-and-information-management-systems/>.

## 5.7 Data collection forms and management

The logic described in 5.6 also applies to data collection forms or CRFs. These are required in order to collect data necessary to monitor participants' progress and safety and, ultimately, for analysis of the trial end points.

The collation of accurate and consistent data is imperative to the success of any trial. Thus the means of data collection requires careful consideration to increase ease of response and precision of reporting.

Forms can be paper or electronic and should be developed with the Trial Manager, Programmer, Statistician and data team. There are some important points to note when developing them:

- Missing data: blank answers should be avoided, especially when relating to the primary outcome. Develop forms that are clearly set out and unambiguous in the instructions. Importantly, time spent on staff training will help reduce the levels of missing data
- Accuracy of data depends on a number of factors: training, accuracy and reliability of the data collectors; the legibility of handwriting; frequency of transcription errors when copying data or records and the accuracy of the data entry clerks.
- Validity depends on whether or not the data have been accurately recorded; the existence of a clear audit trail; recording changes to data and the reasons why will prevent the opportunity to falsify data.
- Yes/no options; this may seem straightforward and many paper forms use a simple tick box but if the question is missed or the answer is 'unknown', a default of 'yes' or 'no' would be wrong, so there is a need to record one of the options.
- Drop-down lists: these rule out the possibility of spelling errors. The preferred option for electronic systems is to have a drop-down list of four options, ie not answered, no, yes and unknown. The

responses can be encoded so that it is easy to differentiate between unanswered questions and where the response is genuinely unknown.

- Free Text: try to avoid free text boxes where possible.
- Free text can be problematic to transcribe from paper to computer. The time taken to interpret/analyse free text can also be vastly underestimated. Where necessary, using a coding frame to code free text as the data is accumulating will make it usable at the analysis stage. Also incorporate an automated spell-checker which includes the appropriate medical terms and medications.
- Multiple-choice questions: on paper it is straightforward to list a number of options and say 'tick one box only'. When transcribing this to an electronic system the method used often depends on how long the wording is for each option and how many options there are – too many will make the screen look cluttered.
- Some paper forms use individual boxes for each character to try to force clarity, especially for names and addresses.

### Data entry checking and validation

The use of computer systems provides more capability to identify and query out-of-range or invalid data at the point of entry. Computer systems can be programmed to identify outlying data or impossible relationships between different data. Determining what is or is not plausible early in the planning phase is crucial and these checks should be built into the computer system.

### Consider the following:

- Ensure that computer input screens and paper records are laid out in a similar manner wherever possible.
- Use clear and unambiguous labels including units of measurement.
- Make the best use of automated data capture, use selective lists as drop-down options to eliminate spelling errors and limit choices.
- Calculate derived values from raw data in the system.
- Clinical data have 'normal' ranges and some systems will query or reject data outside these ranges. However it is important that the system has ranges that reflect the population being studied.

The use of internet-based data management systems facilitate contemporaneous and expedient data monitoring, which means that incorrect or ambiguous data can be corrected promptly, and so improve data quality. Real-time data entry means that the Trial Manager can see an overview of activity in all centres. There is a 'gold standard', which recommends that all data entry to computer systems from paper records should be done twice in order to detect errors. Data entry clerks should not be required to make assumptions or take decisions over whether data are correct. It is therefore very important to have comprehensive data checking and query systems that compare both data entries and produce genuine queries. Where double data entry is not performed, systems should be in place for review of important data at site, e.g. study endpoints.

### Source Data

ICH GCP defines source data as:

*"all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial".*

In essence it is where the data are first captured (either written or electronically). In order to conduct source data verification (SDV) you must be aware of what constitutes source data at a particular site so it is preferable to agree this locally.

More recently, the MHRA accepted that electronic source data are appropriate, provided that there are sufficient means to prove that these have not been altered or amended, or that an audit trail exists to document any changes. This applies to data that are directly input into a computer database, or transferred automatically from another system. This requires the original data record to be date- and time-stamped, with identification of the data entry person and a proper recording system to track changes. The mechanism/process by which source data are extracted or transferred automatically from other computer systems needs to be carefully tested and documented. The systems from which the data are taken should be backed up in the same way as the system for the trial and have the same level of security and data protection. MHRA inspectors or auditors may want to verify that the method of transferring data are secure and provides the required data correctly.

Storage of source data records is also required both during and after the trial. As a result, the filing requirements associated with paper CRFs for a major trial (with thousands of patients over a number of years) are enormous and trials can require huge storage areas for long periods of time. The MHRA has accepted that scanning paper records into a computer system is an acceptable alternative, providing that the computer records are properly indexed and made read-only to avoid tampering. The paper records can then be archived off-site.

## 5.8 Equipment

Always seek advice on hardware and software requirements as these will vary depending on the complexity of the trial; talk to the experts and talk to other trial teams.

Remember: technology changes rapidly – are there sufficient funds in the budget for upgrades during the life of the trial?

- Look at the equipment budget and review what equipment the trial will actually need. You may need a full range of equipment such as computers, network server, printers, fax machines, laptop computers, mobile phones, pagers, scanners, dedicated internal computer network and laboratory equipment. All equipment will need to be PAT compliant so allow time for testing at site or in the coordinating centre.
- The host institution should provide the basics – desks, chairs, lighting and telephones.
- You may not need everything outlined in the budget at the beginning – always check that the host institution is aware of your total needs. The basic infrastructure should be provided by the overheads paid to the institution from the trial funding.

## 5.9 Trial Master File (TMF)/Investigator's Site File (ISF)

A TMF containing all the essential documents to conduct the trial should be set up at the beginning of the trial. The TMF will contain both general trial documents and site-specific documents relating to all of the sites involved and should be held at the coordinating centre. Copies of the general trial documents and site-specific documents for the individual site should be kept at each of the participating sites in the ISF. The files should be kept in a secure but accessible location. All essential documents should be legible and accurate and, where appropriate, should bear the version number, version date and study identification.

Essential documents are those 'documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced', and they serve to demonstrate compliance with the principles of GCP and regulatory requirements. Filing essential documents in a clear and timely manner can greatly assist in the successful management of a trial. They are also the documents that may be audited by the sponsor and the R&D department and inspected by the MHRA (CTIMPs only) in order to confirm the validity of the trial conduct and the integrity of the data collected.

Essential documents required before the trial starts include, but are not restricted to:

- Documents that help you to understand a trial's purpose and methodology and, if appropriate, management structure.
  - ➔ trial protocol and amendments, with signed investigator declaration – agreeing to perform the trial in accordance with the protocol, GCP and applicable regulatory requirements.
  - ➔ protocol amendment log.
  - ➔ sample data collection forms/CRF.
- Documents relating to participants in a trial, for example:
  - ➔ recruitment procedure advert (if used).
  - ➔ informed consent form(s).
  - ➔ participant information leaflet(s).
  - ➔ any other information given to participants, for example, questionnaires.
  - ➔ screening log, identification log, enrolment log.
- Agreements between involved parties, for example:
  - ➔ agreements between sponsor and CI and between sponsor and funder.
  - ➔ signed agreement between sponsor and trial site detailing responsibilities and financial arrangements.
  - ➔ letter of indemnity (non-NHS sponsors only).
  - ➔ funding arrangements. Invoices are trial-related documents that can be included in the TMF or stored elsewhere, but all trial-related documents should be described and their location specified within the TMF, if not included.
  - ➔ scientific approval/peer review, sponsorship letter.

- Documents that record relevant approvals, including approval of any substantial amendments.
  - ➔ REC approval.
  - ➔ MHRA approval (CTIMPs/medical device trials only).
  - ➔ NHS R&D approval/NHS permissions.
  - ➔ Other authorities e.g. ARSAC (for use of radioactive substances).
- Evidence that all trial staff are qualified and authorised to work on a trial, for example:
  - ➔ copies of CVs and honorary contracts relating to all trial staff.
  - ➔ record of training in trial procedures, including copies of up to date GCP certificates relating to all trial staff.
  - ➔ delegation of responsibilities log (kept updated, with dates and signatures of each member of trial staff).
- Information on any laboratory or technical tests to be performed, for example: normal ranges, accreditation of facilities and sample log.
- Detail regarding the specific intervention(s) such as IMP information for a CTIMP:
  - ➔ Investigator’s Brochure, summary of product characteristics or instruction leaflet.
  - ➔ labelling details, handling instructions, certificate of analysis (TMF only) and shipping records.
- Master randomisation list (TMF only), decoding procedures for blinded trials.
- Correspondence between sponsor and site, reports of meetings, for example, site initiation visit.
- Report templates – Site initiation, monitoring, interim and final report templates.
- Other tools which may be needed include: monitoring plan, risk assessment, independent oversight details (e.g. Charters), project plan.

## 5.10 Principal Investigator (PI)/site selection

PI/site selection is crucial to the success of a trial. Selecting PIs who have a known track record in conducting trials is the first step alongside a robust site selection process. Using feasibility questionnaires based on your eligibility and study requirements is recommended. Those sites involved in an external pilot trial are ideal as they have a proven record. However, PIs who come forward and are keen to collaborate in the trial should:

- Be suitably qualified by education, training and experience to assume responsibility for the conduct of the trial; they should have the necessary and appropriate research experience as well as an up to date CV, health professional registration and GCP certificate.
- Have suitable facilities, including pharmacy if IMP storage is required, as well as access to any specialist equipment needed and laboratory facilities.
- Have adequate resources including appropriately qualified staff, sufficient numbers of potential participants and sufficient time to conduct trial – take account of conflicting trials.

Qualifications/experience/facilities/resources must be adequate to enable the PI to conduct the trial safely and properly. The CRN can assist greatly with the identification of potential sites for NIHR portfolio adopted studies. It may be wise to have a number of potential sites on a “waiting list” so they may be quickly included if recruitment dips.

### Site initiation visit/Investigators’ meeting

These may also be termed site training visits and form one of the final few steps prior to starting recruitment. Before a trial starts at a site, ensure that everything is in place including approvals, essential documents and agreements, and that all site staff have been trained in trial procedures and made aware of their responsibilities. The latter is achieved through a site initiation visit and/or a central investigators’ meeting. This covers a review of all documents, a review/demonstration of all procedures and confirmation of planned key dates. Documents should include a summary of the background to the trial; an overview of the protocol requirements including recruitment rate (see also 6.2, trial recruitment); data collection; informed consent procedure; GCP requirements; adverse event reporting; IMP storage and use; plans for monitoring visits and archiving requirements.

## 5.11 Checklist – before recruitment starts

The following is a guide to the essential documents that should be in place in the TMF held at the coordinating centre, followed by a suggested list of documentation, activities and guidance to take place at investigator sites, before recruitment begins.

### Coordinating centre/TMF

#### All trials:

- Confirmation of Sponsorship letter.
- Final approved trial protocol signed by all parties according to local requirements.
- Final approved participant information sheet(s), consent form(s) and GP letter.
- Final approved other written participant information e.g. diary card(s).
- Final approved participant recruitment advertisement (if relevant).
- Research ethics committee (REC) approval.
- NHS permission.
- Final approved risk assessment document and any monitoring plan.
- Sign off from a statistician (if required).
- Signed off/finalised case report forms.
- Signed off/finalised clinical database (if required).
- Systems for managing safety data (e.g. in pharmacovigilance database) agreed and finalised.
- Details of any data monitoring committee or trial steering or management group (if not in protocol).
- Access to all relevant standard operating procedures (SOPs).
- Signed agreements including operational and financial arrangements.
- Statement of insurance to document compensation to participants for trial-related injury (non NHS).
- CVs and other evidence of relevant training (e.g. GCP/regulation/protocol) and qualifications for the investigator(s) and all study team members.
- Normal values/ranges for laboratory/medical/technical tests/procedures.
- Laboratory accreditation(s).
- Decoding procedures for blinded trials.
- Shipping/supply of intervention records (where needed).
- Template logs including delegation logs, screening/enrolment logs, participant identification log, randomisation logs/supply or shipping logs (where applicable).
- Trial start-up/initiation report (or confirmation that site initiation activities have been completed).

**CTIMP trials.** Specific information, in addition to the above, is required:

- Clinical Trial Authorisation (MHRA if in the UK) with any stated conditions addressed.
- Investigator's Brochure or Summary of Product Characteristics (SPC).
- Pharmacy documentation/file.
- All records for Investigational Medicinal Products(s) procurement/supply (e.g. shipping).

### Investigator Site File/ISF

All investigator sites should be provided with all the essential information that constitutes the ISF and guidance regarding set-up activities required:

- Final versions of documentation and copies of all relevant approval letters.
- Relevant indemnity documents.
- Final CTA (for CTIMP).
- All pharmacy arrangements and documentation (CTIMPs only).
- All relevant site agreements and contracts including monetary arrangements.
- Sponsor delegation logs.
- Safety reporting/pharmacovigilance reporting procedures.



- Complete adequate training in trial procedures and GCP.
- If possible, visit the place where recruitment will take place and talk to those who will be recruiting participants.
- Discuss the trial procedures with the researchers and key people from the site to harness their experience and expertise. Involving the clinical team and gaining their support will aid recruitment.
- Agree trial logistics locally and propose ways to optimise recruitment at the site.
- Circulate approved site list.
- Agree a start date for the site.

## 5.12 Managing the budget

Effective budget management is an important part of a trial manager's role. Since most externally funded trials are funded through grant awards with a finite budget, it is essential to plan and monitor expenditure. The initial costings will be calculated with the help of the sponsor's finance department; however it is often the trial manager's role to ensure that the budget is well-maintained.

Practically all trials will have been costed using Full Economic Costing (FEC). However, different funders will award different percentages of costs. Currently, most non-charity-funded grants receive 80% of the FEC costs directly from the funder. The remaining 20% is provided by the host institution from the overhead component of the grant. See 4.1, Planning a grant application for a trial, for more background.

Most external grants allow funds to be vired (transferred) between spending headings, but this should be confirmed with the specific funder. For trials funded on a grant, the Chief Investigator is likely to be the main budget holder. If the trial involves a commercial sponsor or partner(s) they must be involved from the beginning of negotiations and a contract agreed at an early stage.

A budget schedule should be developed based on how and when the money is to be spent. Research costs include staff salaries, materials and equipment, expenses such as travel and payments to contractors/ collaborators. Costs are usually biggest during the implementation phase but may also be significant during trial set-up. Spend should be monitored in comparison with the budget schedule, taking into account actual work completed. Work completed can be determined based on:

- key milestones.
- task completion.
- completed units.
- elapsed time.

The finance department of the host institution is charged with administering the grant. Seek advice, explanations and training in budget management from them and ensure that you have a named finance contact who will be managing the grant. Cultivate a positive relationship with this person; meet them as early as possible to tell them about the trial, keep them updated and talk to them about how you want to manage the budget.

To have the best budgetary control you need to:

- monitor expenditure.
- share good practice.
- assess your trial processes for any savings on a regular basis.
- report regularly.
- think ahead.



## Monitor expenditure

Expenditure should be monitored at a minimum on a monthly basis. To aid this, ensure that there are people within the team with the skills to prepare spreadsheets or use the required computer packages. Also, attend any courses on basic financial management run by the host institution.

Put aside a regular time to deal with financial matters each week/month. Remember always to take a global view of the funding – do not get obsessed with balance sheet accounts. Good practice would be to prepare a spreadsheet of each funding stream (if managing multiple projects) to include start dates, milestones and end dates. Develop processes to monitor spending and to check invoices. Prepare regular financial reports. Your unit may be able to provide you with monitoring printouts for checking. Many host institutions now have online systems for managing budgets, which may avoid the need for bespoke systems. You may need the Chief Investigator to give you access to the institutional system.

## Share good practice

Network both locally and nationally. Locally – if you are based within a CTU – check whether or not special rates for printing and consumables can be negotiated. If you are not in a CTU, contact a nearby unit to ask which suppliers they are using and compare this with the price quoted to the trial. Nationally, share information at key research events, conferences and meetings.

## Assess the trial processes on a regular basis

Consider where cost savings can be made:

- Are there in-house printers/facilities that can be utilised to save money?
- Consider bulk buying as this can often bring a cost saving.
- Consider new suppliers. However, note that your host institution may have purchasing agreements with certain firms and may not allow other firms to contract for work.
- Some items do not attract VAT if they are for medical research. A VAT exemption form is likely to be required – check with the host institution.
- If staff members are constantly doing paid overtime, are there tasks/processes that could be improved or streamlined?
- If participants are to be flagged for data linkage, such as with the NHS HSCIC DLS, collect all necessary data at trial entry as this will save the costs of having to have the participants matched by hand at a later date.
- Consider using teleconferences, Skype™ or webinars instead of face-to-face meetings.

## Think ahead

Contingency should already have been considered when the grant was planned; however, when thinking of spending money, remember that costs may increase over time. If a cost or VAT rate increase is due, order in bulk before the deadline to save money. Also consider whether or not it is feasible to order larger quantities, such as printing questionnaires in bulk to save money. Some funders may only release funds when certain milestones are met – be mindful of this when making purchases. Consider also that costs may decrease.

## Always

- meet the person who will manage the grant on day one and tell them about the trial.
- cultivate a positive relationship with them.
- keep them updated; discuss and understand how the budget will be managed and monitored.
- ensure that printouts from the finance office are sent to the coordinating centre at mutually agreed intervals.
- use funds creatively but within the law and abiding by funder requirements.
- be aware of additional funding streams.
- use economies of scale and combine processes across trials where possible.
- use technologies/lessons learned from previous trials.

Remember: the trial must deliver on time and within budget. Funding supplements are hard to justify and should not be expected.

## 5.13 International trials

Trials that involve international collaboration must comply with national and local requirements. To ensure compliance, it is recommended that you work with a local collaborating group or trials unit.

Some specific areas to consider and to clarify with potential international collaborators:

### **Protocol**

- ➔ is there a system for ensuring ongoing consistency if local versions are required?

### **Local language translations and back translations of PIS/CRFs**

- ➔ is there a need for translation of the whole protocol or just the summary;  
are validated patient administered questionnaires availability in local languages?

### **Regulations**

- ➔ is there a possible requirement of in-country sponsor; what is the level of SDV required?

### **Indemnity arrangements**

- ➔ are there specified levels of insurance cover, wider compensation arrangements?

### **Ethics approvals**

- ➔ is there a requirement for local ethics approval; payment to ethics committees?

### **Local/national permissions**

- ➔ are permissions required from other bodies; differing definitions of non-commercial trial?

### **Safety reporting**

- ➔ requirements of reporting to Eudragilance for EU countries; timelines; reports required?

### **Public involvement**

- ➔ are there different concerns for local population; how to involve?

### **Data management**

- ➔ what is the role of local trials unit?

### **Data protection**

- ➔ clarify use of identifiers, access to clinic records, additional requirements.\*

### **Finance**

- ➔ is there a requirement to reimburse regular clinic appointments and assessments as well as additional visits required by the protocol, payments to participants?

### **Drug supply**

- ➔ clarify labelling, importation procedures and taxes, local availability/provision of drug if commercial stock, lack of trial pharmacists, wider use of community pharmacists, climatic conditions.

### **Clinical practice**

- ➔ are there differing standards of care and protocols?

**Units of measurement to be used**

- ➔ check for standardisation.

**Trial governance**

- ➔ how to involve investigators due to time zones.

**Samples for translational research or validation of study endpoints.**

- ➔ restrictions on exporting samples and different QC systems for laboratories.

\*Different countries have varying levels of protection for personal data. In October 2015, the European Court of Justice ruled that the Commission's US Safe Harbour Decision is invalid as currently US companies cannot guarantee the adequate level of data protection. Thus the personal data of EU citizens may no longer be transferred to the USA because of the implications of the US Patriot Act; this will be of particular concern in studies collaborating with institutes in the USA. The courts will be working to resolve this issue.

# Section 6 During the trial

During the trial, there are several activities and processes being undertaken. Many of these can be carried out in parallel.

## 6.1 Trial Master File/Investigator Site File

The purpose of the TMF and ISF is described in Section 5. During the course of the trial, the TMF and ISF should be kept up to date by including the following essential documents:

- New versions of the essential documents described in the previous section; old versions should be marked 'superseded' with the date from which this is effective and kept in the file.
- Approvals of substantial amendments.
- Records of any protocol violations or deviations.
- Records for any new staff.
- Records of correspondence/meetings with sites.
- Monitoring visit reports.
- Source documents, site file only.
- Signed, dated and completed CRFs and corrections.
- Safety reports.
- Records of trial governance including TSC, TMG, DMC minutes and papers.
- Documentation on key decision making and trial conduct (including email discussions).
- Annual progress reports including REC, MHRA.
- IMP accountability.
- Records of any tissue samples collected.
- Subject screening log.
- Signed consent forms, generally site file only, but may be collected centrally with the consent of participants.
- Subject ID code list, site file only.

Keep the TMF index updated with references to where documents are held (particularly important for documents held electronically or held by different parties, e.g. statistician).

It is good practice to maintain a summary document or tracking log detailing initial approvals and subsequent amendments of protocol, PIS and other essential documents.

## 6.2 Trial recruitment

Make recruitment as simple as possible, with clear instructions. Carefully plan the recruitment process, always considering:

- where participants will be recruited.
- who will recruit them.
- who will provide consent; for example, the participant (if adult with capacity) or a proxy (if a minor).
- when this will take place.

### Training

Prior to the start of recruitment, provide training for the site staff, such as Principal Investigators and research nurses, who will be responsible for recruitment. This can be a group event, or individual training conducted during a site initiation visit (SIV) or by webinar to ensure that the appropriate team members are fully informed about the trial and the paperwork. Spending time with site teams before they start recruiting to the trial should improve the quality of the data collected and reduce the number of data queries generated later. Provide clear written instructions for team members. This will depend on the nature of the trial but may take the form of a detailed manual of operations or a study flowchart that clearly outlines tasks and responsibilities. An operations manual facilitates communication and can also standardise training. A slide set can also be provided to the site for internal training of new staff. Always encourage team members to contact you if they have any queries. Try to meet new investigators and site staff who come on board throughout the trial or arrange to meet them at conferences or other key events.

## Golden rules to ensure optimal recruitment

- Keep work for investigators and other site staff simple and minimal.
- Plan and target marketing strategies and site visits effectively.
- Review the impact of these strategies.
- Always be polite and demonstrate professional courtesy.
- Respond quickly to queries.
- Be enthusiastic.
- Use all methods of communication as appropriate to maintain regular contact with all sites:
  - ➔ telephone
  - ➔ email
  - ➔ publication and letters
  - ➔ website
  - ➔ newsletters
  - ➔ personal contact
  - ➔ webinars

## Ideas to consider to ensure optimal recruitment

- Contact relevant voluntary organisations and charities and other patient groups for advice on how to raise awareness. Include text for these third party websites or newsletters in the ethics submission.
- Consult membership lists/networks of relevant colleges, professional organisations or disease areas.
- Place flyers in journals to encourage interested investigators.
- Attend relevant conferences to lobby opinion leaders and set up satellite meetings to promote interest.
- Produce a 'starter pack' for investigators and nurses to launch recruitment.
- Produce a list of 'frequently asked questions'.
- Refer to online sources for recruitment strategies e.g. the ORRCA project (Online Resource for Recruitment research in Clinical trials).

## Monitoring recruitment targets

In order to monitor recruitment and adapt plans as required you should:

- set realistic targets based upon feasibility for both numbers of participants and numbers of centres – review regularly.
- monitor screening activity via screening logs as these logs will give an overview of trial activity and uptake in recruiting centres, identifying and enabling exploration of reasons for non-recruitment.
- change activities if necessary – monitor their impact and change things that do not work.
- be open-minded – think laterally.
- motivate site staff by reminding them about the importance of the research and patient benefits.
- try to factor in or pre-empt periods of low recruitment; for example, regular changes in hospital staff, holiday periods or seasonal presentation of diseases or medical conditions.
- where appropriate, advise recruiting sites to consider staggering recruitment to aid the management of timely follow-up.

## Communication strategies

- Regular newsletters to all investigators: name individuals/centres who have achieved high recruitment or reached an important milestone.
- Individual feedback to centres: praise recruitment and express appreciation.
- Branding: relevant tokens of appreciation, mugs, post-its, pens, mouse mats, key-rings and trial-specific items have proved useful.
- Attend conferences with trial-specific literature; take an exhibition stand.
- Recruitment awards, for example for reaching a milestone, for example the 100th patient, all help to maintain interest and motivation for the trial but need to be of low value and approved by the TSC.
- Email countdowns over the last few months of recruitment to build excitement and aid push towards the recruitment target.
- Teleconferences with the research nurses to share ideas.

## Encourage ownership by investigators

- Publish the protocol.
- Encourage presentations by different stakeholders.
- Try to publish on substudies or novel approaches, for example, recruitment strategies as a group to keep trial interest high.
- Arrange meetings and attendance at conferences.
- Visit centres that are recruiting well and those that are not – learn what works and what does not.

## Centres with poor recruitment

- Discuss what the issues are and consider how to resolve them.
- Seek advice on the potential barriers to recruitment from a patient perspective.
- Telephone calls and visits can be more effective than emails.
- Discuss and share recruitment tips from high-recruiting sites.
- Maintain communication with research networks – send regular recruitment updates and discuss any difficulties with individual sites.

## If recruitment is not going well, consider

- is the question still relevant?
- do the eligibility criteria need reviewing?
- are investigators still interested?
- are participants prepared to join?
- are procedures appropriate and flexible?
- closing some centres and/or adding more centres – this action should be considered in the context of your understanding of barriers to recruitment. It may be that alternative strategies/corrective actions in your current open centres may improve recruitment and avoid the time and resource associated with identifying and opening new centres.

## 6.3 Retention and follow-up

- Provide each site with a report listing due dates of follow-up and acceptable time windows.
- Make sure the patient information leaflet clearly outlines what trial participation and follow-up entails.
- Consider the aims of the trial, the population under investigation and the resources available.
- Make sure you have all the necessary permissions and appropriate consent, such as ethics, NHS Health and Social Care Information Centre, NHS Personal Demographics Service.
- Make sure you have the necessary consent and required identifiers for follow-up through central registers if there is a possibility you might use these (eg. longer term-follow-up or anticipated loss to follow-up).
- Make sure participants know what follow-up entails by including details in the patient information leaflet.
- Organise systems and plan when the next contact with the participants should be made.

Other ideas that may be appropriate include:

- Notifying the participant by letter or text when contact is due, including reminders (e.g. if fasting is required for the study visit assessments).
- Rearranging the appointment if the participant does not respond or attend clinic.
- If appropriate to the research topic and participant population, using birthday cards, anniversary cards/Christmas cards.
- Using participant newsletters (approved by ethics committees).
- Using a variety of communication methods appropriate to that particular participant group.



If you do not get a response, think about another way you could get the data, especially primary outcome data. This may require amendments to permissions and approvals but could include:

- a questionnaire to the participant's GP.
- HSCIC and Information Services Division (ISD) Scotland for hospital admissions and death details.
- a shortened questionnaire including just the primary outcome data for participants reluctant to complete a full-length questionnaire.
- collecting primary outcome data over the telephone if the participant does not return their questionnaire.
- focusing on ensuring that follow-up at the final trial visit/final questionnaire is completed where interim visits have been missed or interim questionnaires have not been completed.

### Participant questionnaire response rates

A Cochrane Systematic Review published in 2009<sup>34</sup> presented a number of effective strategies to increase response to postal and electronic questionnaires. These included: contacting participants before sending a postal questionnaire; sending postal questionnaires by first-class post or recorded delivery and providing a stamped-return envelope; making questionnaires, letters and emails more personal and keeping them short; offering incentives, see [Cochrane Database Syst Rev 2009;3:MR000008](#).

## 6.4 Data collection and management

### The trial web portal

The Trial Manager is usually involved in the design and building of the trial website, in collaboration with the programming team. There are 'off the shelf' versions available or bespoke systems that can be built for a specific trial. Websites are only useful if they are built to a professional standard, maintained and kept up to date. A poorly designed, out-of-date website can be detrimental to a trial's progress. It often falls to the Trial Manager to ensure that trial materials on the website are correct and up to date.

## 6.5 Data protection – the practicalities

### Day-to-day management

Collect only data fit for purpose and approved by an ethics committee and included in your institution's registration under the Data Protection Act 1998.<sup>4</sup>

- Ensure adequate security and restricted access to paper records.
- Ensure adequate security and restricted access to electronic records by use of password-protected systems on a secure network with back up and audit trails.
- Ensure appropriate consent is obtained.
- Ensure that information held on participants is anonymised/unlinked as soon as practically possible, depending on the trial design. This may be when an individual's data collection is complete, and it is considered that the risk of emergency unblinding is minimal.
- Document the reason for the timing of anonymisation of data.

### Simple solutions – paper

- Store securely, ideally in locked fireproof filing cabinets.
- Never leave data accessible overnight or take out of the office.
- Plan access and archiving procedures with your host institution or sponsor.

### Simple solutions – electronic

- Restrict access to password-protected systems.
- Password-protect email systems.
- Use a daily back-up – stored off-site.
- Avoid personal identifiers in email correspondence.
- Use encryption for personal data, coded identifiers.

Always consult your institution's information governance manager/policy for guidance.

## 6.6 Monitoring

Monitoring involves overseeing the progress of the trial in order to confirm that:

- the rights and well-being of participants are protected.
- the data are accurate, complete and verifiable from source documents, where the source document is not the CRF itself.
- the trial is conducted in compliance with the current approved protocol, SOPs, the principles of GCP and regulatory requirements.

The extent and nature of monitoring should be proportionate to the risks to participants, the organisation and/or data quality and results, as determined in the trial risk assessment carried out at the planning stage. Further considerations that may influence the risk and monitoring are the objectives, purpose, design, complexity, blinding, size and endpoints of the trial. The trial monitoring plan will be determined by the sponsor(s) and the central team. It will describe what will be monitored and how this will be done, i.e. central or on site. For more information on developing an appropriate monitoring plan, see the Clinical Trials Toolkit [www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring](http://www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring).

Monitoring while the trial is on-going should include the following:

- Confirmation of participant consent – check signed consent forms either during site-monitoring visit or when received centrally.
- Review of eligibility criteria before randomisation.
- Review of primary outcome data.
- CRF validation, either during site monitoring visits or when received centrally, i.e. review of CRFs for legibility, completion by correct person, missing data, internal consistency and consistency with other trial data. Queries should be clarified with site staff and corrected.

It may also include:

- Site monitoring visits to review the ISF and ensure that training, resources and facilities remain adequate. For example; review of IMP storage, dispensing, accountability and review of inventories of sample storage at site.
- Source data verification during a site monitoring visit to compare data recorded on the CRF with clinical records in order to identify any errors of omission or inaccuracies. This usually concentrates on key data such as eligibility criteria, adverse events and primary endpoint data.
- Central statistical monitoring to identify unusual data patterns that may require further investigation and verification of data against external sources.<sup>35</sup>

If a site monitoring visit is performed, a report should be written summarising what was reviewed, with a description of the findings and actions, before filing in the TMF.

Monitoring should be performed by someone with appropriate scientific/clinical knowledge who is familiar with the IMP, protocol, documents given to participants, GCP and applicable SOPs and regulatory requirements.

In addition to the documents maintained during the trial, the following essential documents should be added to the TMF/ISF after the end of the trial:

- Documentation of IMP destruction.
- Audit certificate – TMF only if performed.
- Close out documentation (completed by site or report of close out visit).
- End of trial notification and reports – REC, MHRA.
- Archiving documentation – paper and electronic.

## 6.7 Preparing for audit and inspection

### Definition of audit

In the context of research, an audit is 'A systematic and independent examination of trial-related activities and documents to determine whether or not the evaluated trial-related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)' (ICH-GCP Section 1.6).

### The audit process

Audits are usually internal planned processes conducted by the organisation or sponsor of the trial. Information is exchanged freely throughout the process between the auditor and the individual or organisation being audited. Results should be used internally to train staff and improve the conduct of research. Internal audits will often be conducted in advance of an external inspection as part of the preparatory process. Many of the activities undertaken in preparation for an audit will overlap with those required for an inspection.

### Definition of inspection

In the context of trials, an inspection is 'The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies)' (ICH-GCP Section 1.29).

### The inspection process

Regulatory inspections are formal processes with legal consequences if non-compliance with the regulations is identified. The MHRA implemented a fully risk-based inspection process from October 2009. The majority of organisations conducting trials are encouraged to complete a compliance report once every 2 years. Information obtained from this report is considered, alongside prior inspection history and any organisational changes, to determine the organisation's management of their risk. The MHRA then classifies each organisation as high, medium or low risk. Organisations assigned the highest levels of risk are prioritised for routine inspections. Although completion of the compliance report is not mandatory, organisations that do not submit a report will automatically be classed high risk.

### Types of inspection

There are three types of GCP inspection:

**Routine inspection:** inspections of the systems and procedures used to conduct clinical research in the UK of trials sponsored by both commercial and non-commercial organisations, in order to assure compliance with applicable legislation.

**Triggered inspection:** ad-hoc inspections that may be triggered as a result of MHRA licensing requests or reports received by the MHRA on suspected violations of legislation relating to the conduct of trials. In some cases, these inspections can be unannounced and a plan may not be provided to the organisation in advance.

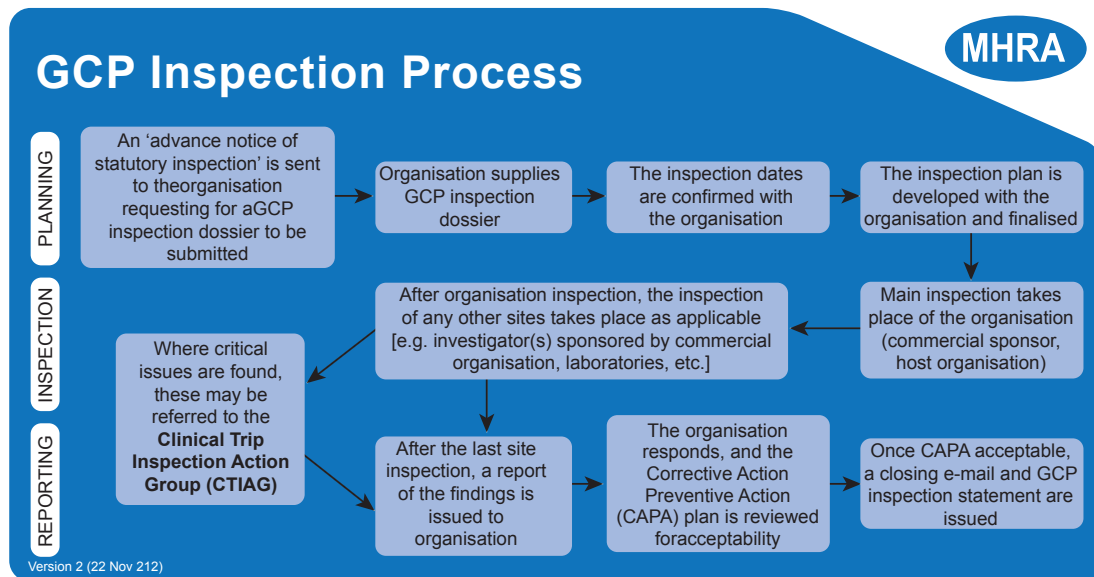
**Committee for Medicinal Products for Human Use (CHMP):** requested inspections resulting from central marketing authorisation submissions. The CHMP can request GCP inspections in relation to marketing applications made using the EU centralised procedure.

### Notification of a routine inspection

The organisation or site is sent a preliminary notification informing them that they have been selected for a formal routine inspection. At this stage, the organisation is asked to provide more information on the activities they perform by completing a dossier. The dossier should include a list of all trials, an index of all SOPs, organisation charts, selected SOPs and an overview of trial procedures and key service providers. Once the dossier has been returned, the inspection date is confirmed to the organisation and the inspection plan is developed.

## Purpose of the routine inspection

The MHRA will inspect all processes involved in the conduct of the trial to establish whether or not they are effective, being followed, continually reviewed and improved, consistent with GCP and the applicable legislation. A primary goal of the inspectorate is to ensure that the rights, safety and well-being of the participants are protected and that the scientific and data integrity of the trial is maintained. See MHRA GCP routine inspection process diagram below:



## What preparation is required for a routine inspection?

Alongside the preparation and submission of the dossier, other key preparatory activities to consider are:

- Appoint an inspection coordinator to act as the lead contact responsible for all communication with the MHRA relating to the inspection.
- Identify all CTIMPs, including those closed to recruitment or follow-up. Use the algorithm 'Is it a Clinical Trial of a Medicinal Product?' if clarification is required. See [www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/317952/Algothrim.pdf](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf).
- Determine who the sponsor is for all trials and review whether older trials fall within the remit of the regulations.
- Review previous and common findings and identify areas of risk.
- Establish a work plan, prioritising important issues.
- Develop a communication plan to inform relevant internal departments and researchers as early as possible. Ensure that appropriate staff members are made aware of the need to be available for interview, and that they are sufficiently prepared by holding inspection training days and mock interviews. Update training records, ensuring that they include regulatory, SOP and trial-specific training undertaken.
- Review essential documentation; ensure that all required documents, listed in ICH-GCP section 8.0.15 are present and easily located and divided into sections within the TMF or ISF. A 'milestone summary' is useful at the front of each file. Any missing documents should be recorded on a file note, with an explanation.
- Access to the database if electronic data capture is performed, or the inspectors may request a printout of eCRFs. Participants' medical notes and all completed consent forms should also be made available for review on the day of the inspection.
- Confirm that all regulatory, ethical and local approvals, including a EudraCT number for trials that commenced after 1 May 2004, were obtained prior to the trial start.
- Review document tracking and version control processes – ensure that all versions of essential documents are present and that outdated versions are clearly marked as superseded. A 'change summary' is useful for essential documents such as patient information leaflets and consent forms.
- Ensure that the staff delegation log is up to date, reflects the current situation and is signed by the Investigator. Signed and dated CVs should be available for all past and present staff listed on the log.
- Confirm the whereabouts of the documentation and data for any archived trials and ensure that written information from the archive site is available, that the data are stored in accordance with data protection legislation.

- Audit or monitor premises, services and trials that may be selected for inspection.
- Develop corrective and preventative action plans for any potential deficiencies identified and include a timeline for implementation. Ensure that notes to file are up to date. These may be reviewed by the MHRA during the inspection.

Consider the need for any further system development and prepare an action plan if necessary. Major changes should not be made prior to the inspection, as time will not allow for appropriate training and implementation.

### What will happen during a routine inspection?

Routine inspections consist of site visits to the Organisation and, where appropriate, to selected investigator sites. They will begin with an opening meeting at which the Lead Inspector will describe the purpose and goals of the inspection, introduce the Inspector(s) and confirm the Inspection Plan. Ideally, the Chief or Principal Investigator should be available to greet the Inspector(s) and a member of the Organisation should accompany them at all times during the course of the inspection.

A number of trials are usually targeted for an in-depth review of the TMF. The Inspectors may request additional documentation during the inspection, and these should be readily and rapidly available. It is helpful to designate a 'runner' for each day of the inspection, who will be responsible for locating any requested documents. A list should be maintained of all additional documentation provided to the Inspector.

Interview sessions with relevant staff will be undertaken, generally in accordance with the Inspection Plan. Ensure that a member of the team is present to record all questions asked and answers provided, specifically noting any additional follow-up or clarification required. Do not provide additional information voluntarily and if the answer to a question is not known, agree to provide clarification at a later stage.

### What will happen after a routine inspection?

At the end of the inspection there will be a closing meeting at which the findings are reported verbally. A written inspection report will follow within 6 weeks and will classify deficiencies identified during the inspection or during post-inspection review as 'critical', 'major' or 'other'. You are required to respond to the Inspector(s)' report including timelines and proposed changes within a specified time.

Further information about the MHRA inspection process is available from the MHRA website at [www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#inspections-under-the-risk-based-compliance-programme](http://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#inspections-under-the-risk-based-compliance-programme).

## 6.8 Drug management systems

- If the drug/intervention is being provided by the Coordinating Centre, a distribution management system is essential. If clinical centres have no stock of trial drug/intervention and trial associated documentation, they cannot recruit into the trial.
- Effective drug management is particularly important in an international multicentre trial. All trial documentation and instructions will need to be in local languages.
- A system for independently testing a random sample of drug packs prior to distribution, especially if the Trial is placebo-controlled, should be developed to ensure the contents of numbered intervention packs match the allocation code. Using a local trials pharmacist or biochemist to carry out this testing can be cost-effective.
- A system for the destruction of unused trial drugs, during and at the close of the trial, and of any expired drugs will need to be developed early in the planning stage.
- Distribution methods need to be reliable, economical and budgeted for.
- All trial drug packs distributed will need to be accounted for at the close of the trial.

A reliable and easy-to-use system is critical for international trials, especially where a drug is being exported to different sites. Any drug/intervention information leaflets and/or instructions need to be in all local languages and approved by local regulatory bodies. Translations need to be done by a reputable translation service or the local Principal Investigator. Back-translation into English is highly recommended to ensure that there has been no misunderstanding of the information.

**Remember:** if the trial involves a drug and the coordinating centre is providing specialised labelling for the trial intervention, ALWAYS consult a Trial Pharmacist in the host institution, or the MHRA.



## Unblinding/unmasking

It is essential that there are systems in place to ensure that only essential unblinding is carried out and procedures are in place for what should be done in the event of unintentional unblinding. This helps to ensure that the integrity of the trial is protected and investigators and trial team are not influenced by knowledge of the intervention.

In general, unblinding should only be done if:

- further clinical management is dependent on the knowledge of which intervention was allocated, for example, if this information is necessary to inform ongoing medical care. This is also known as emergency blinding. If there are concerns about side effects but there is no clinical need for knowledge of the trial intervention for future management, it can be stopped or interrupted temporarily or permanently without unblinding.
- reporting to regulators or pharma collaborators of potential SUSARs.
- at the request of the DMC.
- during any unblinded analysis as specified within the trial analysis plan.
- at the end of the trial to determine the effect of the drug/intervention.
- in some circumstances it is ethical to unblind at a participant's request; for example, in a trial of a common intervention such as antibiotics, a participant may have side effects that are sufficiently serious that they do not want to be prescribed the drug again.
- ideally the randomisation codes should be held centrally by an independent unit or person, for example randomisation service or 24-hour pharmacy, and details of this should be specified in the trial protocol. Unblinding should be available 24 hours a day, 7 days a week, but it should be noted that this can be expensive and will need to be accounted for in the trial budget.
- all unblinding requests should be controlled with a gate-keeping process, for example criteria for unblinding or refer-on process. In most cases the gate-keeper would be the trial coordinating centre or CTU. Ultimately, the Chief Investigator is responsible for ensuring the trial blinding and integrity is maintained. However direct access must also be provided for emergencies.
- records of ALL participants unblinded and the reason for unblinding should be kept on a confidential central system. The trial team should not have access to these data.

## 6.9 Safety management and reporting systems

### Safety reporting

It will not be possible to predict when any expedited safety reporting may be required. It is therefore very important that staff in the central office and participating sites are familiar with reporting requirements and procedures. Clarity is required on reporting timelines and responsibilities. Written guidance on processes is required, including what safety data are being collected, what constitutes a Serious Adverse Event (SAE), who has authority to unblind/unmask a trial participant and the role of the sponsor. A flow chart can be a useful tool to visually describe processes.

For trials evaluating a medicine that falls within the scope of the UK Regulations and the EU Clinical Trials Directive, there is a need for effective and sustained input from pharmacy. Pharmacies to be used in a trial must be assessed in the same manner as one would assess a site prior to start-up. Pharmacy initiation should occur as close as possible to the start, ideally during the site initiation visit.

It is now common for a Pharmacist to be a grant holder and a member of the TMG. The Trial Manager will work closely with the Chief Trials Pharmacist in developing and documenting the trial procedures relating to pharmacy. Typical documents produced include the dispensing procedure, drug accountability log, prescription sheet, labels and a description of the process for drug destruction.

The manufacture, packaging, labelling, distribution, prescription, secure storage and accountability of randomised trial medication are all issues that, while the ultimate responsibility of the sponsor, the Trial Pharmacist and the Trial Manager will need to be familiar with. The Trial Pharmacist at each site is usually assigned responsibility for site drug management in close liaison with the Sponsor. Procedures for the recall of any drug/intervention are to be in place prior to the start of the trial.

In publicly funded trials, the medications may be supplied from one or more central locations, and distributed to local pharmacies. It is the local pharmacy that then ensures that the correct medication for the allocated randomised group is given, which means that the pharmacy often needs to know the randomised allocation.



This type of communication needs careful oversight, and it may be that the task of implementing systems such as a Trial Pharmacy SOP, and ensuring responsibility of the oversight falls to the Trial Manager. It is the Trial Manager's responsibility to ensure that local pharmacy staff are adequately trained on the trial protocol and pharmacy-related procedures.

The Trial Manager may well be the natural point of contact during the conduct of the trial for all pharmacies as they raise issues, or simply in the routine transmission of information on drug stocks and supplies used to facilitate efficient stock control and resupply. When undertaking site visits, pharmacy staff should always be included in any meetings.

The Trial Manager is centrally involved in reviewing any suspected deviations from the protocol, from issues such as suspected overdoses through to misallocation of intended randomised medication. A description of the responsibilities of a trial pharmacist should be included in the trial protocol and SOPs. In addition, the Pharmacy Trial File should contain all relevant information specific to a trial, including code-breaking/unblinding procedures.

### Pharmacovigilance systems

In order to comply with regulations and guidelines pertaining to pharmacovigilance, organisations responsible for pharmacovigilance for a trial must ensure that they have implemented systems that allow for the adequate recording, reporting, evaluation and onward reporting of adverse events in each trial undertaken. This includes:

- Setting an appropriate timeframe for which adverse events are actively reported in compliance with the regulations.
- Clear instructions in trial protocols with regard to what adverse events should be reported, the time frame for reporting and the reporting mechanism.
- Creating CRFs that capture adverse events as specified in the protocol and that allow site investigators to record their evaluation as to whether or not a causal relationship between the adverse events and the trial treatment(s) is likely.
- Ensuring that trial sites have received training on the safety reporting requirements via site initiations and investigator meetings.
- Performing periodic safety reviews of aggregate trial safety data by TMG and/or DMC.
- Creating and updating internal SOPs.
- Checking compliance with protocol and SOPs through monitoring and internal audits.

### Serious Adverse Events

Arrangements for Serious Adverse Event (SAE) reporting and evaluation are detailed in the European Commission's Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') published in EudraLex Volume 10.<sup>36</sup>

Site investigators are required to report all protocol-defined SAEs immediately to the Sponsor. The protocol, trial SOPs and delegation logs should detail reporting timelines and responsibilities.

The regulations allow trial protocols to specify SAEs that do not require immediate, expedited reporting as SAEs by site investigators, if the event is one of the main outcomes in the trial such as disease progression in trials measuring progression-free survival or disease-related deaths in mortality trials.

For CTIMPS, the trial should be set up on eSUSAR (MHRA) for reporting of SUSARs.

Further information about definitions and reporting requirements of adverse events can be found on the HRA website ([www.hra.nhs.uk](http://www.hra.nhs.uk)).

## Section 7 End of Trial

End of trial occurs once all data are received ready for analysis and reporting. Depending upon the length of follow-up, this can be a long time after the trial closes to recruitment. A definition of the end of the trial should be specified in the protocol. The Sponsor, Funder, REC and, if appropriate, MHRA, will be aware of the end of trial date.

In most cases, the end of trial will be the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol. The final analysis of the data and report writing is normally considered to occur after formal declaration of the end of the trial.

### 7.1 Extension of end of trial

To extend a trial beyond the agreed end date (as specified in the trial protocol), you may need to apply to the Funder/Sponsor for an extension. This can be a funded or a non-funded extension. Such applications should be made well in advance of your planned end date and be approved by the TSC prior to submission. The Funder will need to see good, clear, justifiable reasons for any extension. If the trial is funded as part of a wider programme (such as NIHR Programme Grants for Applied Research [PGFAR]) it may be possible to extend recruitment within the existing grant without requesting an extension from the Funder. Consideration should be given, however, to knock-on effects of this to other timelines within the grant.

If the end of trial date is extended, all relevant approvals should be obtained (using the IRAS centralised system). In addition, all investigators and the Sponsor should also be notified.

### 7.2 Close out plan

A close-out plan should be developed very early in the lifecycle of the trial. This will include timelines and responsibilities for the tasks described below. This should also include information about the responsibilities and timing of data analysis and the database lock.

### 7.3 End of the recruitment period

Trial recruitment will close either as per protocol or prematurely. If the latter, it should be upon the recommendation from the DMC endorsed by the TSC or by the trial TSC, in the absence of a DMC. Ensure that the randomisation system has been disabled at the end of recruitment.

### 7.4 Early termination or temporary suspension of the trial

A trial can be terminated early if the DMC and TSC agree that there are safety concerns or it is unethical to recruit further participants, i.e. the treatment effect is definite with a smaller population.

If the trial is terminated early, or is temporarily suspended, the REC and the MHRA should be notified within 15 days of closure.

The Sponsor should be notified immediately.

All investigators must be informed using expedited means of communication. The reasons for early termination or temporary suspension should be explicit.

### 7.5 Planned closure

#### Informing investigators

Unless recruitment to the trial is stopped early, the investigators should be given plenty of warning that the recruitment phase is drawing to an end in order to enable them to ensure that all patients can be randomised before close. When recruitment closes, all investigators should be aware of any ongoing obligations to the trial. These obligations can include providing further data and archiving; continuing obligations should be pre-specified in the site agreement.

Investigators should be informed of end of trial via a letter or other suitable form of communication from the Trial Manager or the Chief Investigator. This should:

- thank the Investigator for their participation.
- summarise patient status – number of withdrawals, deaths, SUSARs and SAEs.
- remind the Investigator of any continuing trial obligations, for example informing local personnel, archiving and availability of data for queries arising after end of trial.
- arrange for the return of trial supplies and/or drug supplies, if applicable.
- advise of the possibility of audit or inspection, if applicable.
- outline the results of the trial or provide a copy of the trial report (if available).
- inform the investigators, if possible, of the expected timing of publication.

### Informing participants

Participants should be informed of the end of trial where possible. This should be discussed and agreed by the TSC. HRA guidance on informing participants is available: [www.hra.nhs.uk/documents/2015/08/hra-guidance-end-study-pis-v4-1\\_20-august-2015.pdf](http://www.hra.nhs.uk/documents/2015/08/hra-guidance-end-study-pis-v4-1_20-august-2015.pdf).

### Informing the Sponsor

The Trial Manager should ensure that the Sponsor has been informed that the trial has reached its defined end date.

### Informing the Research Ethics Committee and MHRA

The REC which gave the favourable opinion of the research must be notified in writing of end of trial. The appropriate form should be emailed to the REC within 90 days of the end of the trial. A summary of the final research report should be sent to the REC within 12 months of end of trial. There is no standard format for final reports.

For trials that also required MHRA approval, a Declaration of the end of a Clinical Trial form should be sent to the MHRA within 90 days and a summary of the final research report sent within 12 months of end of trial. In addition the dataset should be uploaded onto the EudraCT database.

## 7.6 Site close-out

Once the trial is completed at site, check that the site file contains all essential documentation, resolve final data queries, confirm the archiving arrangements (see Section 9) and check IMP accountability/destruction. Close-out can either be done remotely or by conducting a site visit.

Final close-out of the trial can only be done once the TMF and site files are confirmed as complete. Sites should be clear on arrangements for archiving; this will usually be specified within the contracts/agreements signed off early in the trial.

## 7.7 For CTIMP trials: trial drug supplies

An agreement should be made as to where and how trial medication should be handled. Unused trial supplies will usually be either returned to the coordinating centre or destroyed on site. The Trial Manager should ensure that sites/pharmacies are aware of the requirements for the end of trial and that proof of destruction is received and recorded in the TMF by the Coordinating Centre in a timely manner.

## 7.8 Financial closure

When the trial closes to recruitment, the Trial Manager will have a role in ensuring that all recruitment payments to sites have been made. Reimbursement may also be made after the follow-up period on return of clean and complete CRF data. In addition, the Trial Manager should check that any payments due to third party suppliers (eg couriers, IMP supplier) have been made.

# Section 8 Preparation of final reports and publication

When final analyses have been conducted, the final reports should be prepared. This will involve the preparation of publication(s) and the final reports for the Sponsor/Funder the REC and the MHRA, where applicable.

The team should be involved in the preparation of the publications and reports, which is usually led by the Chief Investigator. It is important to clarify who will be responsible for each section; a plan should be discussed and agreed in advance of any deadlines, especially for final reports.

The exact requirements for final reports and deadlines for submission vary and the guidance given by the Sponsor/Funder should be followed. Attention should be paid to the specific requirements associated with this to allow sufficient planning.

A summary of the final research report should be sent to the main REC (and MHRA for clinical trials of investigational medicinal products) within 12 months of the notification of the end of the trial. There is no standard format for final reports to the REC. As a minimum, you should inform the REC whether or not the trial achieved its objectives, the main findings, and arrangements for publication or dissemination of the research, including any feedback to participants. For clinical trials of investigational medicinal products the Sponsor is responsible for uploading the end of trial summary results to EudraCT as per the European Commission's guidelines<sup>1</sup> on posting and publication of result-related information. You don't need to submit your clinical trial summary report to the MHRA, however the MHRA also provides instructions on their website about how to confirm submission of the results to them.

## 8.1 Publication and dissemination

### Trial results

The results of a trial must be published, whatever the outcome. It is scientific misconduct not to aim to publish the trial results.

It is common practice to set up a subgroup of the TMG as a 'writing committee' who produces initial drafts. Both the interim and the final report are reviewed/approved (as appropriate) by the TMG and TSC.

Most public funders of research require notification of any manuscripts or other research outputs, such as conference presentations and press releases, prior to publication. A copy should be submitted to the Funder prior to submission, taking into account the Funder's timescale for review. Funders must be appropriately acknowledged with the use of a logo and/or statement of support or disclaimer as appropriate in all outputs.

Prior to signing any journal copyright or disclaimer forms, you should check your Funder's/Sponsor's policy on this and take appropriate advice.

Prior to submitting any trial results that may have Intellectual Property (IP) Rights, the Sponsor, Funder and any local IP representatives should be consulted.

Participants should be informed of the trial results. This could, for example, be via a letter, a plain English summary on the trial website, or newsletters to participants. You should also consider disseminating the results more widely, for example, through participating centres, GP practices, patient groups, voluntary organisation newsletters or hospital outpatient departments. It is important to publish in formats and media accessible to trial participants. Involve your trial PPI representatives or an appropriate organisation to obtain guidance and input on how to present the information for this population.

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<sup>1</sup> Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006

## Data sharing

It is recognised that sharing of individual patient data (IPD) from clinical trials can advance clinical research for the benefit of patients. The approach to data sharing should be considered in the development stages of the trial if a policy does not already exist. A set of good practice guidelines for the sharing of IPD and associated documentation from publicly funded clinical trials has been produced by the Hubs for Trials Methodology Network and is available on their website ([www.network-hubs.org.uk/advice/network-guidance/](http://www.network-hubs.org.uk/advice/network-guidance/)). Whilst this document is primarily aimed at publicly funded clinical trials units, it provides a useful reference for the development of procedures for handling the sharing of IPD.

## Authorship

Arrangements for authorship should have been agreed in the pre-trial set-up phase and agreed by the TSC. Any change to the authorship policy must be agreed by the TSC.

## Confidentiality and consent

Information that may identify individual participants should not be published, including written descriptions or photographs, unless the information is essential for scientific purposes and the participant, or parent or guardian, gives consent. In such cases, the person involved is shown the draft manuscript.

If the paper is to have group authorship and intends to name Principal Investigators and/or other local research staff at the end of the paper, then consent for such acknowledgement should be obtained from every individual prior to publication. It is advisable to obtain this consent early on in the trial or by trial closure at the latest.

## The Consolidated Standards of Reporting Trials (CONSORT) statement

CONSORT encompasses various initiatives developed to alleviate the problems arising from inadequate reporting of RCTs. The main product is the CONSORT statement, which is an evidence-based minimum set of recommendations for reporting RCTs.

The CONSORT statement comprises a 25-item checklist and a flow diagram along with brief descriptive text. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting and aiding critical appraisal and interpretation.

All respected journals request that papers conform to the CONSORT format for reporting randomised trials. See [www.consort-statement.org](http://www.consort-statement.org).

Extensions of the CONSORT statement have also been developed for the following types of design: interventions and data including cluster trials, non-inferiority and equivalence trials, pragmatic trials, herbal medicinal interventions, non-pharmacological treatment interventions, acupuncture interventions, harms and abstracts.

## Dissemination of trial results

It is important to establish whether participants want to be actively informed of trial results or whether they would like the onus to be left with them to obtain them. Patient and public involvement in the trial may help guide this. Whenever possible, the results should be shared with all investigators and participants before public release, either orally or in writing.

Presentation of the trial results at national and international conferences should be planned well in advance of the results being available. Once you know the date that the results will be available, you should identify key conferences around that time.

The timing of the publication of results at conferences and the publication in the journal must be checked with the Funder and journal editor.

Press releases on trial results or transmission via social media outlets are cost-effective promotion. Contact the press offices of the Funder, NHS sites and universities involved in the trial.



## Section 9 Archiving

The documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced are defined as essential documents; these are held in the Trial Master File (TMF) which may be paper, electronic or both.

These documents should be filed in an organised way in the TMF and careful consideration given to how key decisions and timelines are recorded to allow evaluation of the trial conduct. This will facilitate trial management, audit and inspection.

Archiving applies to all paper and/or electronic documents which evidence the conduct of the trial; these may be held by the investigator sites and/or the Central Trial Office. Essential documents must be retained and archived for sufficient periods to allow for audit and inspection by regulatory authorities, and should be readily available upon request. The Sponsor and the Investigator must ensure that the documents contained, or which have been contained, in the TMF are retained after the end of the trial. There are different time-periods depending upon the type of trial; refer to the Sponsor for guidance and for CTIMPs Directive 2005/28/EC Article 17). There are a number of important considerations when archiving:

### Facilities

- Are the facilities adequate e.g. do they protect sufficiently against fire and flood?
- How much will it cost to archive? Are there sufficient funds available in the grant?
- Are the facilities secured so that unauthorised access is prevented?

### Named archivist

- For CTIMPs it is a legal requirement for the Sponsor to name an individual to be responsible for archiving; this person is responsible for checking the facilities are appropriate, controlling and keeping a record of access to the archive (e.g. in the form of a log recording what is held in the archive, tracking and retrieving of documents on loan from the archive).
- Access to archives should be restricted to authorised personnel. Any change in the ownership or location should be documented in order to allow tracking.

### Site documentation

- Is the responsibility of the investigator at site and should never be sent to the Sponsor in order to prevent uncontrolled access by the Sponsor to the Investigator files.
- It is acceptable for the Sponsor to organise for a third party to archive the Investigator site files as long as access to these remains restricted to the investigator and/or host institution (not the sponsor).
- If the Investigator is no longer able to maintain custody of their essential documents, the sponsor should be notified so that alternative arrangements can be made.
- When involving a third party archive company appropriate contractual agreements transferring responsibilities under the Data Protection Act 1998<sup>4</sup> should be signed and a check made of the original consent to ensure there are no precluding factors.

### Electronic data

Electronic data should be stored in a format that permits viewing in generic software, avoiding the need for dependence upon specific software that may not be available or accessible in the future. Appropriate back up of electronic data must be considered to mitigate against the risk of failure of storage media.

### 9.1 Destruction of essential documents

Reasons for destruction of essential documents should be documented and signed by a person with appropriate authority. This record should be retained for a further defined period as appropriate. A certification of destruction should be obtained if using an outside contractor.



# Additional Sources of Information

## (by date of publication)

This is a non-exhaustive list of additional sources of information regarding trial management and trial conduct. The authors of this Guide are not responsible for the accuracy of these documents.

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