

A Guide to Efficient Trial Management

Trials Managers' Network



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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.

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, Welsh Government, or Health & Social Care in Northern Ireland).

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 National Institute for Health Research (NIHR) and approval by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC).

All enquires should be directed to NETSCC in the first instance.

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Commonly used terms

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.

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 The NIHR Clinical Research Network makes it possible for all patients and health professionals across England to participate in relevant clinical trials.

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. In addition, most CTUs will have expertise in the coordination of trials involving investigational medicinal products, which must be conducted in compliance with the UK Regulations governing the conduct of clinical trials resulting from the EU Directive for Clinical Trials.

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

Coordinated System for gaining NHS Permission (CSP) Standard process for adoption onto NIHR Portfolio of Studies in order to access NIHR Clinical Research Network (CRN) support and funding; streamlines the process for gaining NHS permissions by collating the information for global and local approvals; researchers initiate this in the Integrated Research Application System (IRAS) by completing and submitting the CSP application form.

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

Good Clinical Practice (GCP) A set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. See ICH-GCP.

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.

Indemnity Compensation for damage, loss or injury.

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.

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 printed or submitted for this single system (includes REC, R&D, MHRA, Gene Therapy Advisory Committee).

International Conference on Harmonisation (ICH) (Europe, USA, Japan) The body that defines standards for the terminology, design, conduct, monitoring, recording, analysis and reporting of research. These standards give assurance that the reported results are accurate and credible and that the rights, integrity and confidentiality of all participants have been protected throughout. Section E6 of ICH defines principles of good clinical practice (referred to as ICH-GCP). Research teams on a Clinical Trial of an Investigational Medicinal Products (CTIMPs) in the UK must follow GCP requirements as detailed in Medicines for Human Use (Clinical Trials) Statutory Instruments; all non-CTIMP studies conducted within the NHS adhere to GCP according to the Research Governance Framework (RGF).

International Standard Randomised Controlled Trial Number (ISRCTN) 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.

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 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.

Investigator Brochure A compilation of clinical and pre-clinical pharmacological/biological data relevant to the use of that IMP(s) in human subjects (one single brochure for all trials using the same IMP).

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

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, 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 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, 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, the conduct, the management or the 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.

Patient and Public Involvement 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.

Participant/Patient information leaflet 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.

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

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) Department of Health guidance for the conduct of research within the NHS in England (refer to second edition, 2005).

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

Serious Adverse Event (SAE) Any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

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-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 a 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.

Statutory instrument (SI) A document that defines UK law in on a specific topic; for example, SI (2004/1031) The Medicines for Human Use (Clinical Trials).

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 causal relationship with the IMP.

Trial Master File (TMF) File with 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.

Introduction

Background

The first edition of the TMN *Guide to Efficient Trial Management* was produced in March 2000. The third edition was last produced in 2006. It is from this third version that the current group of volunteers working within trials research from all over the UK have come together to produce the new edition.

Purpose

The 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.

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 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 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 standard¹ as they aim to minimise potential biases 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.

Allocation is independent of the characteristics of the participants, unless the allocation uses stratification or minimisation; see *Randomisation methods*, below, and 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 such as centre or country in a multicentre trial. Blocked randomisation must be 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 (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 ignorant of the intervention allocation.
- **Single blind** – either the participant or the investigator is unaware of the intervention allocated. Usually it is 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.

1.4 Placebos

Placebos are dummy interventions often used in drug trials. 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.

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, 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 slightly larger than required sample size to allow for dropouts or poor adherence. Similar calculations can be made for other types of outcomes such as 'means'. 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, 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 the range of effect sizes around the estimate for the trial that is likely to include the true value. Commonly, a 95% confidence interval is used, giving a 95% chance that the true value is within this interval, but 80%, 90% and 99% are alternatives.

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.

A trial comparing participants allocated intervention 'a' versus those allocated intervention 'a' plus intervention 'b' in parallel is not confounded for the evaluation of intervention 'b', as this is the only difference between the regimens.

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.

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.

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 sent 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.

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

1.10 Types of 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 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
- are not usually placebo controlled.

Phase II: 'feasibility'

Phase II trials are performed on larger groups of 100–300 participants and are designed to assess how well the drug/intervention works, as well as to continue Phase I safety assessments in a larger group of volunteers 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.

Phase II is sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements and how much should be given. 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, 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
- aim to provide evidence of activity and better evidence of safety
- aim to define dosage and regimen
- may or may not be randomised and/or placebo-controlled.

Phase III trials

Phase III trials are randomised controlled multicentre trials on large patient groups of 300–3000 or more depending on the disease/medical condition studied, 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
- 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.

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 a 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.

Section 2 National infrastructure

2.1 National Institute for Health Research, England

The vision of the National Institute for Health Research (NIHR) is to improve the health and wealth of the nation through research. The NIHR provides the NHS with the support and infrastructure it needs to conduct first-class research. It funds a broad range of research infrastructure in the NHS England (see the list of key NIHR infrastructure facilities at www.nihr.ac.uk/infrastructure/Pages/default.aspx).

2.2 UK Clinical Research Network (UKCRN)

Clinical Research Networks (CRN) have been established in each of the four UK nations, funded by the UK health departments. Together, these national networks form the UKCRN.

The structure of the networks varies between each country, but all share the common goal of providing the infrastructure to support high-quality clinical research studies for the benefit of patients. There is a commitment to ensure that the CRN 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 CRN provide the necessary support and facilities the NHS needs for first-class research that results in high-quality care for patients and the public.

In practice, this means:

- providing researchers with advice on the feasibility of studies, to ensure that they can be practically delivered through the NHS
- running systems to streamline the bureaucracy associated with gaining permission to run a trial in the NHS, and reducing the set-up time for trials
- 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 their 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.

National Institute for Health Research Clinical Research Network

Through the NIHR CRN in England, researchers working on trials included in the NIHR portfolio have access to a wide range of support at the planning, set-up and delivery phases of research. For more information, see the research journey interactive map available from the researchers' web pages of the Clinical Research Network Coordinating Centre website at www.crncc.nihr.ac.uk/researchers/researchers.

What does the CRN provide for trial managers?

- Support for trial planning.
- Support for trial set-up.
- On-site help to identify and recruit patients.
- Advice on alternative recruitment sites.
- Training in Good Clinical Practice (GCP).

- Help to manage the Research Passport scheme.
- Free ISRCTN (International Standard Randomised Controlled Trial Number) registration for eligible NIHR portfolio studies.

2.3 UK Clinical Research Collaboration (UKCRC)

All clinical research carried out in the UK is currently supported by a national infrastructure, the UKCRC. The UKCRC provides a forum that enables all partners including main funding bodies, government, charities, academia, the NHS, regulatory bodies, industry and consumers, to work together to transform the clinical research environment in the UK.

The forum promotes a strategic approach to the identification of opportunities for, and obstacles to, clinical research and their resolution. In so doing, the UKCRC aims to benefit the public and patients by improving national health and increasing national wealth. For more information, go to the UKCRC website at www.ukcrc.org.

2.4 UKCRC Clinical Trials Unit Network

Clinical Trials Units (CTUs) are an important element of the UK-wide clinical 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. They have the capability to provide specialist expert statistical, epidemiological and other methodological advice and coordination to undertake successful trials. In addition, most CTUs will have expertise in the coordination of trials involving investigational medicinal products (IMPs), which must be conducted in compliance with the UK regulations governing the conduct of trials resulting from the EU Directive for Clinical Trials.²

CTUs that have been awarded UKCRC registration are required to demonstrate 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 had established robust systems to ensure conduct and delivery of trials to the highest quality standards.

Further details about the CTU functions and services can be found at the UKCRC-registered CTUs network website (www.ukcrc-ctu.org.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/or 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*
All trials	<ul style="list-style-type: none"> Guidelines for GCP Department of Health Research Governance Framework for Health and Social Care 2005³ Data Protection Act 1998⁴ Freedom of Information Act 2000⁵ Mental Capacity Act 2005⁶ (non-CTIMPs only) Human Tissue Act 2004⁷ (only if collecting human tissues) 	<ul style="list-style-type: none"> Ethics approval (*NRES/NHS/HSC Research Ethics Committees) NHS Permissions (NHS/HSC R&D offices) The NRES is now part of the Health Research Authority (www.hra.nhs.uk)
In addition, for clinical trials of medicinal products	<ul style="list-style-type: none"> Medicines for Human Use (Clinical Trials) Regulations 2004⁸ and its amendments 2006a,⁹ 2006b,¹⁰ 2008¹¹ and 2009¹² 	<ul style="list-style-type: none"> MHRA approval
In addition, for clinical trials of medical devices	<ul style="list-style-type: none"> The Medical Devices Regulations 2002¹³ The Medical Devices (Amendment) Regulations 2012¹⁴ 	<ul style="list-style-type: none"> Trials involving non-CE-marked medical devices and CE-marked medical devices used for novel indications MHRA approval
Other	<p>*Depending on the specifics of your trial, you may also require approvals from the following review bodies:</p> <ul style="list-style-type: none"> Administration of Radioactive Substances Advisory Committee Gene Therapy Advisory Committee Ministry of Justice Health Research Authority (included components of work undertaken formerly by the National Information Governance Board) National Offender Management Service Social Care Research Ethics Committee <p>Expert Advisory Group/the Commission on Human Medicines review for certain first in human trials</p>	

Good clinical practice – all trials

Good clinical practice is an international ethical and scientific quality standard for the design, conduct recording and reporting of research involving humans.

The International Conference on Harmonisation (ICH), which brings together the pharmaceutical industry with the regulatory authorities of the EU, Japan and the USA, developed guidance on GCP in 1996.¹⁵ The purpose is to provide assurance that:

- data and reported results of clinical investigations are credible and accurate
- rights, safety and confidentiality of participants in clinical research are respected and protected.

It is internationally recognised as good practice, but is not enforced by law in most countries.

With the advent of the Medicines for Human Use (Clinical Trials) Regulations 2004⁸ and the EU Directive on Good Clinical Practice,² compliance with the principles of GCP became a legal obligation in the UK/Europe for all trials of investigational medicinal products (see 3.1.7, *Clinical Trials of Investigational Medicinal Products*) as well as recognised good practice for clinical trials of any type of intervention.

Principles based on Articles 2 to 5 of the Good Clinical Practice Directive

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.
3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.
4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.
5. The available non-clinical and clinical information on an IMP shall be adequate to support the proposed clinical trial.
6. Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.
7. The protocol shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.
8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.
9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

Conditions based on Article 3 of the Good Clinical Practice Directive

1. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.
2. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.
3. A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.
4. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with the Data Protection Act 1998⁴ are safeguarded.
5. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor, which may arise in relation to the clinical trial.

[Taken from the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.]⁹

Research Governance Framework for Health and Social Care

The Research Governance Framework (RGF) for Health and Social Care³ has been drawn up by the Department of Health for England and aims to bring together general principles of good practice and to ensure that all research undertaken within health and social care organisations conforms to a common set of standards.

As such, it is applicable to all research within the remit of the Secretary of State for Health for England and includes clinical and non-clinical research; research undertaken by NHS or social care staff using the resources of health and social care organisations; and any research undertaken by industry, charities, research councils and universities within the health and social care systems that might have an impact on the quality of those services (see *Table 2*).

TABLE 2 Research Governance Framework's aims and applicability

Research governance:	Aims to improve research quality and safeguard the public by:	Applies to everyone who:
<ul style="list-style-type: none"> • sets principles, requirements and standards • defines mechanisms to deliver standards • describes monitoring and assessment arrangements 	<ul style="list-style-type: none"> • enhancing ethical and scientific quality • promoting good practice • reducing adverse incidents and ensuring lessons are learned • preventing poor performance and misconduct 	<ul style="list-style-type: none"> • designs research studies • participates in research • hosts research in their organisation • funds research proposals or infrastructure • manages research • undertakes research

Data Protection Act 1998

The Data Protection Act 1998⁶ applies where any 'personal data' are being collected, held or processed. Under the definitions of the Act, 'personal data' means data that relate to a living individual who can be identified:

- from those data, or
- from those data and other information that are in the possession of, or is likely to come into the possession of, the data controller, and includes any expression of opinion about the individual and any indication of the intentions of the data controller or any other person in respect of the individual.

The Data Protection Act places obligations on those who process information (data controllers) while giving rights to those who are the subject of those data (data subjects). 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. Sensitive personal data include the state of individuals' mental or physical health; their religious, philosophical or political beliefs; trade union membership; their criminal record; their racial or ethnic origin; and details of their sexual life.

The Data Protection Act stipulates that personal information should not be used for the purposes of research without the approval of the individual. The only exception to this is in situations deemed by the State to be in the best interest of the patients and public at large.

In practice for most trials, consent to collect, store and process information is covered in the informed consent process.

The Data Protection Act sets out principles that must be applied to the use and storage of those personal data.

Most health care research requires the processing and/or storage of personal and sensitive information relating to living individuals and is therefore governed by the Data Protection Act 1998. The requirements of the Data Protection Act are encompassed in the eight Data Protection Principles, which form part of the Act. Please note that the common law duty of confidentiality also applies.

The eight principles of data handling are that data should:

1. be collected fairly and lawfully
2. be processed for limited purposes
3. be adequate, relevant and fit for purpose
4. be accurate
5. be kept for no longer than necessary
6. be processed in line with the data subject's rights
7. be stored securely
8. not be transferred to countries without adequate data protection.

To help ensure compliance:

- Register under the Data Protection Act with your host institution.
- Consider if waivers are required for collaboration outside the EU.
- Consult with Information Commissioner if there is any uncertainty about process.
- Ensure confidentiality clause in staff contracts.
- Develop procedures for breaches of confidentiality.
- Ensure that staff are aware of data protection protocols within the coordinating centre.
- Identify lead person for data protection issues.
- Participants must give consent to process all personal information.
- Participants must be given accurate information regarding the use of data/samples collected both now and in the future.

The Freedom of Information Act 2000

The Freedom of Information Act 2000⁵ gives individuals a general right of access to information held by or on behalf of public authorities. It is intended to promote a culture of openness and accountability among public sector bodies, and therefore to facilitate better public understanding of how public authorities carry out their duties, why they make the decisions they do, and how they spend public money.

Any person who makes a written request to a public authority for information must be informed as to whether or not the public authority holds that information and, subject to exemptions, be supplied with that information. The public authority must reply promptly, not later than the 20th working day following receipt of the request for information, and in the format requested.

More information and guidance, including frequently asked questions, is available from the Information Commissioner Office's website (www.ico.gov.uk).

The Mental Capacity Act 2005

The Mental Capacity Act 2005⁶ is relevant to research involving adults over the age of 16 years in England and Wales, [except CTIMPs – the Medicines for Human Use (Clinical Trials) Regulations 2004⁸ make legal provision for participation in CTIMPs by adults lacking the capacity to consent]. In Scotland, the Adults with Incapacity (Scotland) Act 2000 applies.¹⁶ There is no specific legislation in Northern Ireland; however, there is the common law of consent.

The parts of the Mental Capacity Act that are relevant to research came into force on 1 October 2007. The basic principle is that incapacitated adults should not participate in research where the same results could be obtained from adults with capacity. However, this act allows participation where the incapacity is related to the research in question.

The Mental Capacity Act provides the legal arrangements to enable adults lacking capacity to consent to take part in research other than CTIMPs, including health and social care research, that would otherwise require the participant's consent. The Mental Capacity Act also enables adults with capacity to make arrangements or make their wishes known in advance in order to deal with future situations where they might lack the capacity to consent to take part in research.

Participants who lose capacity during the trial

Loss of capacity in participants taking part in CTIMPs is governed by Schedule 1 of the Medicines for Human Use (Clinical Trials) Regulations 2004.⁸ Where a capable adult consents but later becomes incapacitated, management of these participants is described in the protocol but the original consent endorses the loss of capacity, providing that the trial is not significantly altered.

For all other research, when submitting the Research Ethics Committee (REC) application, the research team must include what steps they will take in the event of a participant losing capacity during the trial. There are currently four options:

- withdrawal of the participant and anonymisation of tissue/data
- withdrawal of participant, retention of identifiable tissue/data
- participant remains in the trial
- not applicable as informed consent will not be sought from any participants.

The Human Tissue Act 2004

The Human Tissue Act 2004⁷ 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. Notably, the Human Tissue Act regulates certain activities such as the transportation of organs, post-mortem and anatomical examinations, and the storage of human material for education, training and research purposes.

Consent from the donor or nominated representative is the fundamental principle of the Human Tissue Act, and underpins the lawful removal, storage and use of body parts, organs and tissue. Different consent requirements apply when dealing with tissue from the deceased and tissue from the living.

The Human Tissue Act established a regulatory body called the Human Tissue Authority (HTA) to regulate the activities concerning the removal, storage, use and disposal of human tissue.

Tissue that is relevant must be stored in a licensed tissue bank or meet an exemption for storage. One exemption is tissue being collected in an ethically approved trial.

There is separate legislation in Scotland: the Human Tissue (Scotland) Act 2006.¹⁷ 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 via the HTA legislation, policies and codes of practice web pages. Practical help with the legislative and good practice requirements relating to the use of personal information and human tissue samples in health care research in the UK is available via the Data and Tissues Tool Kit (www.dt-toolkit.ac.uk).

Clinical Trials of Investigational Medicinal Products (CTIMPs)

The EU Clinical Trials Directive (2001/20/EC)¹⁸ 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*).⁸

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).

The Clinical Trials Directive has attracted some criticism^{30,31} for causing many organisations involved in clinical trials to take a risk-averse approach to meeting the regulatory requirements, resulting in greatly increased costs and complexity, particularly for non-commercial trials. In 2011, a Medical Research Council/MHRA/Department of Health joint project developed and released a risk assessment framework and guidance on risk-proportionate approaches to the management and monitoring of clinical trials.³² The guidance focuses on the risks inherent in a trial protocol that impact on participant safety and rights, and the reliability of the results.

A two-part assessment is suggested: first, a simple IMP risk categorisation based on marketing status and standard medical care and; second, an assessment of the trial design, population and procedures to identify specific areas of vulnerability. Type 'a' trials, using a licensed product within the scope of its licensed range of indications, dosage and form or off-label use that is established practice, may use a new 'Notification Scheme' that expedites the process of obtaining a CTA. Type 'a' trials are also eligible for a number of risk adaptations that simplify the management of the trial, such as simplified labelling, pharmacovigilance, IMP management and trial documentation.

Please also note that clinical trials that fall under the EU Clinical Trials Directive (2001/20/EC)¹⁸ and the Medicines for Human Use (Clinical Trials) Regulations 2004⁸ must also adhere to the RGF for Health and Social Care.

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 2002.¹³

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 14155,³³ should be adhered to in order to guarantee a high standard of quality.

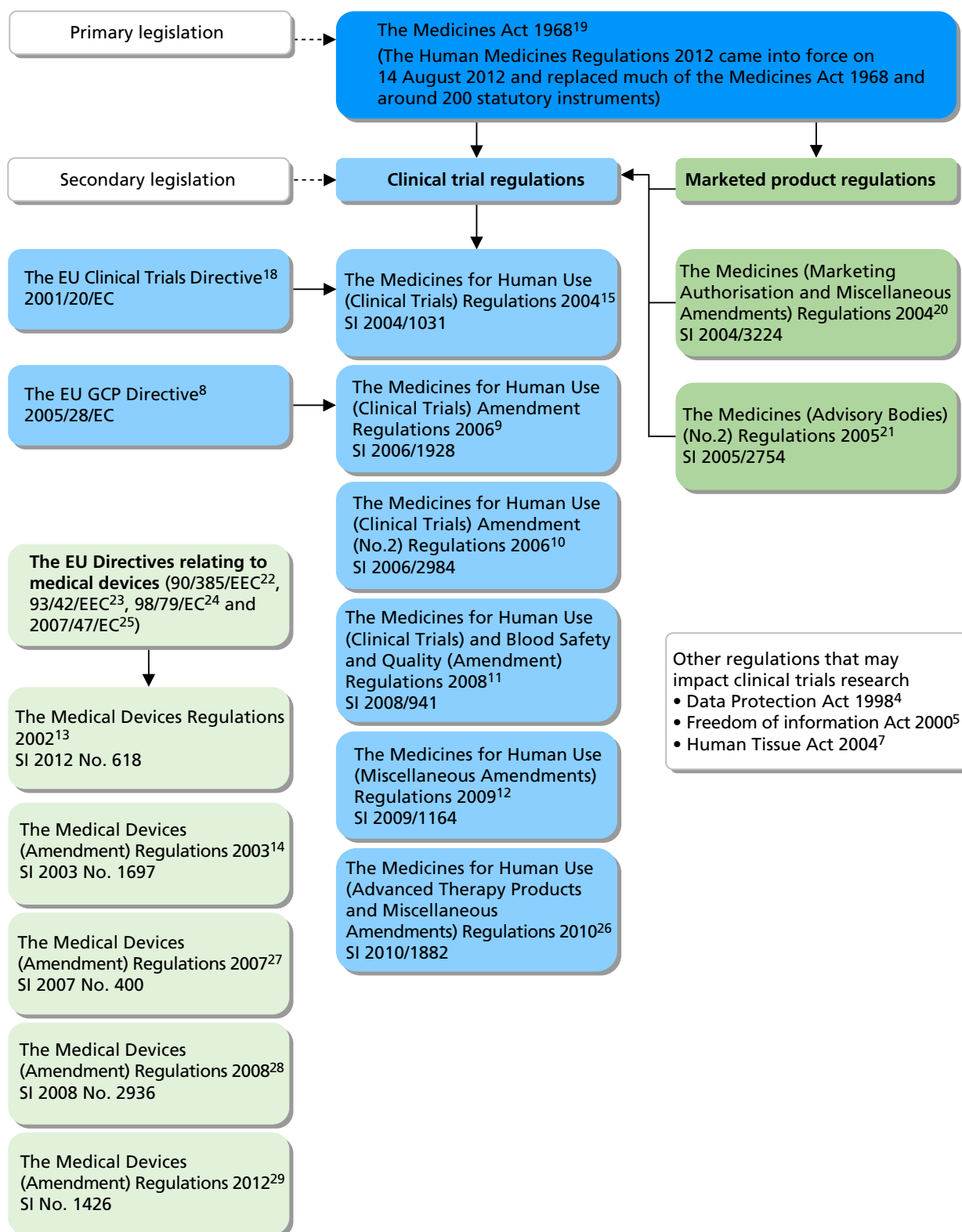


FIGURE 1 Key regulations relevant to CTIMPs and medical devices in the UK.

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 (Figure 2).

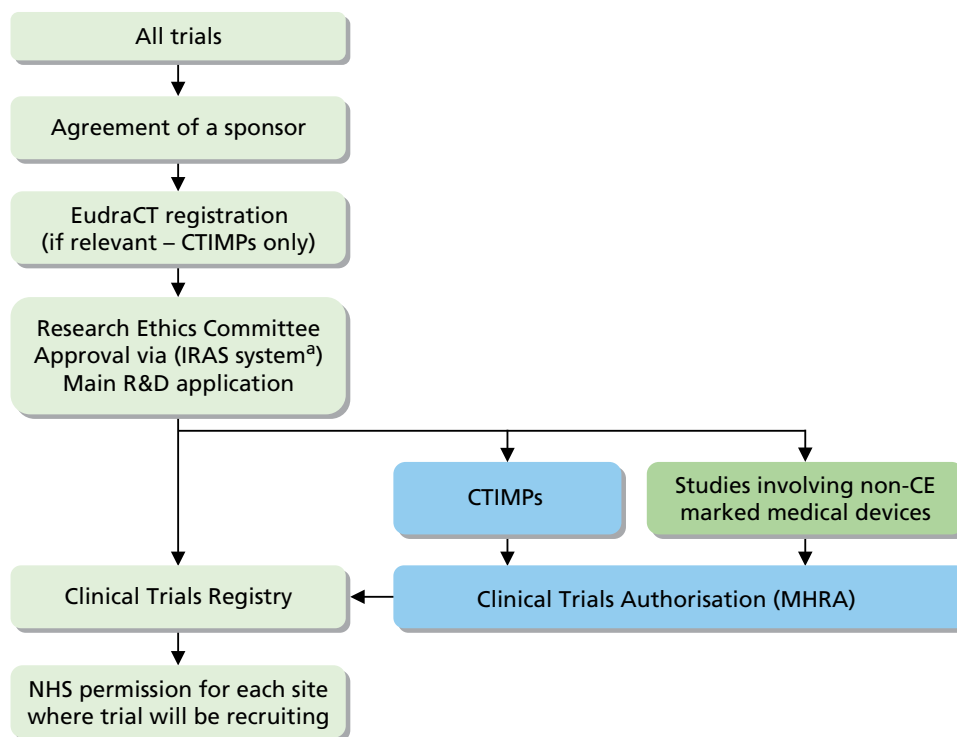


FIGURE 2 Approvals, permissions and registrations needed before a trial can commence in the UK (these steps may be done in parallel). *Please note that applications for the Clinical Trial Authorisation, Ethics Committee Approval and NHS permission can be submitted in parallel through the IRAS. EudraCT, EU Clinical Trials Database.

Chief Investigator checklist (before seeking approvals)

Before seeking approvals, the following checklist should be completed:

- Sponsor(s) identified and agreements for allocation/delegation of responsibilities, if necessary, are in place.
- Arrangements for appropriate patient and public involvement.
- Input from a statistician secured.
- Peer review complete.
- Arrangements for a Data Monitoring Committee (DMC), Trial Steering Committee (TSC) and/or management group in place, with consent from members.
- Trial risk assessment carried out, trial management systems and monitoring plan/arrangements in place.
- Funding secured.
- Unique trial number and/or EU Clinical Trials Database (EudraCT) number obtained (as appropriate).
- Research and Development (R&D) and local NHS support departments, for example pharmacy, laboratories, and radiology, consulted and capacity confirmed.
- Contracts and agreements in place including third-party agreements where outsourcing of any trial specific test/services is required.
- Insurance and indemnity arrangements in place (non-NHS).
- CVs of investigators (signed and dated).
- Arrangements for trial supplies in place.

- Arrangements for pharmacovigilance considered.
- Systems in place to ensure trial will be conducted in accordance with the principles of GCP and Clinical Trials Regulations.
- Trial Master File established.
- Protocol and associated documents:
 - EudraCT number on all documentation.
 - End of trial defined.
 - Safety reporting section of the protocol outlining definitions and reporting requirements.
 - All written information provided to/viewed by subjects, such as participant information sheets, consent forms, patient diaries and recruitment advertisements in a finalised and version-controlled format.
 - All other relevant trial documentation finalised and version-controlled, for example questionnaires, case report forms, Trial-Specific Operating Procedures (TSOPs).
 - Investigator's Brochure or Summary of product characteristics (SmPC) developed/identified.

A PDF copy of the checklist can be obtained from the Clinical Trials Toolkit (www.ct-toolkit.ac.uk/routemap/ci-checklist-before-seeking-approval).

Sponsorship

All clinical research within the scope of the RGF requires a sponsor(s). 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. This is normally the case in commercial trials where the main funder is the sponsor. The sponsor often contractually delegates tasks to other parties.

In most non-commercial trials, the sponsor is normally one of the organisations taking the lead for particular aspects of the arrangements for the trial. Sponsorship of non-commercial clinical research is commonly taken on by universities, as employing organisation of the Chief Investigator, and NHS trusts, i.e. provider of health and social care.

For further information and summary of sponsorship responsibilities, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004,⁸ see the Clinical Trials Toolkit Sponsorship Station (www.ct-toolkit.ac.uk/routemap/sponsorship).

Ethics 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 ethics approval.

NHS ethics approval is obtained using the centralised system called IRAS (Integrated Research Application System). Up-to-date information on how to apply for ethics committee approval can be found on the Health Research Authority (HRA) website. The website covers guidance on completion of the ethics application and gives detailed guidance on the writing of trial documents such as patient information leaflets and protocols, and gives clear advice on documents that need ethics approval. In addition to this, the National Research Ethics Service (NRES) also advises on informed consent procedures – for capable adults, incapacitated adults, minors and emergency situations.

Further information and guidance about consenting procedures are available from Centre of Research: Ethical Campaign (<http://corec.org.uk/welcome-to-centre-of-research-ethical-campaign>).

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 following review bodies:

- The Administration of Radioactive Substances Advisory Committee (ARSAC) (www.arsac.org.uk).
- MHRA (www.mhra.gov.uk).
- Ministry of Justice (www.justice.gov.uk).
- NHS/Health and Social Care R&D offices.
- NRES/NHS/Health and Social Care Research Ethics Committees.
- National Information Governance Board for Health and Social Care (www.nigb.nhs.uk).
- National Offender Management Service (www.justice.gov.uk/about/noms).
- Social Care Research Ethics Committee (www.srec.org.uk).

A 1-hour IRAS training e-module suitable for anyone doing health and community care research can be accessed.

Further information and guidance are available from the IRAS submission guidance at www.myresearchproject.org.uk/help/submissionguidance.aspx#2.

Clinical trial registration

Clinical trial registration is not mandatory for *all* trials but the Department of Health's 'registration of clinical trials and public access to findings' policy strongly encourages voluntary registration of trials and other well designed studies on publicly accessible registers such as ISRCTN and ClinicalTrials.gov.

In addition, the HRA has made trial registration a condition of ethical approval and has published information and guidance on this.

The International Committee of Medical Journal Editors (ICMJE) requires that trials that meet the following definition be registered on a publicly accessible database to be considered for publication in ICMJE journals: 'Any research study that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome (URL: www.icmje.org/about.html and URL: www.icmje.org/clin_trial.pdf).'

The ISRCTN Register (<http://isrctn.com>) is the Department of Health-recommended register for NIHR portfolio studies, and complies with the requirements set out by the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/about/en) and the WHO 20-item Trial Registration Data Set (www.who.int/ictrp/network/trds/en/index.html).

The ISRCTN is a simple numeric system for the identification of clinical trials worldwide. The randomly generated, eight-digit ISRCTN is unique to a registered trial, thereby 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.

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.

The NHS R&D standard application form can be obtained from IRAS. It is possible to complete applications for both ethics approval and NHS permission simultaneously by using the online application process. The R&D application is assessed by the CRN.

Coordinated systems for gaining NHS permission for clinical research have been implemented across the UK. The systems are compatible and they were designed to facilitate studies in which sites are in different parts of the UK. The system available will depend on where the lead NHS R&D office is based.

In England, the NIHR Coordinated System for gaining NHS Permission (CSP) is the system designed to support the application and approvals process for NHS R&D approval for NIHR CRN portfolio studies. These include commercially-sponsored studies which are actively adopted into the NIHR CRN portfolio, and studies funded through NIHR infrastructure.

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

1. England: NIHR CSP (www.crnc.nihr.ac.uk/about_us/processes/csp/index).
2. Scotland: NHS Research Scotland Permissions Coordinating Centre (www.nhsgrampian.org/nhsgrampian/nrspcc.jsp?pContentID=7170&p_applic=CCC&p_service=Content.show&).
3. Wales: NISCHR Permissions Coordinating Unit (www.wales.nhs.uk/sites3/page.cfm?orgid=952&pid=52006).
4. Northern Ireland: Health and Social Care Application Gateway (http://c.ymcdn.com/sites/tmn.site-ym.com/resource/resmgr/TMN_Guide/contact_detailsNI.pptx).

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.

Additional requirements for CTIMPs

For a trial testing or evaluating a CTIMP there are a number of additional steps to follow before a trial can commence.

Step 1: confirm that the trial falls within the scope of the Medicines for Human Use (Clinical Trials) 2004 Regulations.⁸ The MHRA has developed an algorithm to help researchers determine whether or not a trial falls within the scope of the Medicines for Human Use (Clinical Trials) Regulations. A PDF version of the MHRA clinical trials algorithm and some mock examples can be found at the MHRA website [see *Clinical trials for medicines: Is a clinical trial authorisation (CTA) required?* www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/IsaclinicaltrialauthorisationCTArequired/index.htm].

Step 2: sponsors are required to register the trial on the EudraCT and obtain a unique EudraCT number as a component of the Clinical Trials Authorisation Process. The EudraCT number becomes the main identifier for the trial and should be used in all correspondence with the MHRA, ethics committees and when reporting issues and developments such as amendments and SUSARs.

Step 3: complete a risk assessment and identify the IMP category for the trial. The CTA application form is completed using the IRAS website (www.myresearchproject.org.uk). Clinical trials of medicinal products in human subjects require authorisation by the competent authority (MHRA). This authorisation is granted in the form of a CTA (see *Figure 3*). Further information and guidance is available from the MHRA web pages (see *Clinical trials for medicines: Applying to conduct a clinical trial*) and the CTA submission station of the Clinical Trials Toolkit.

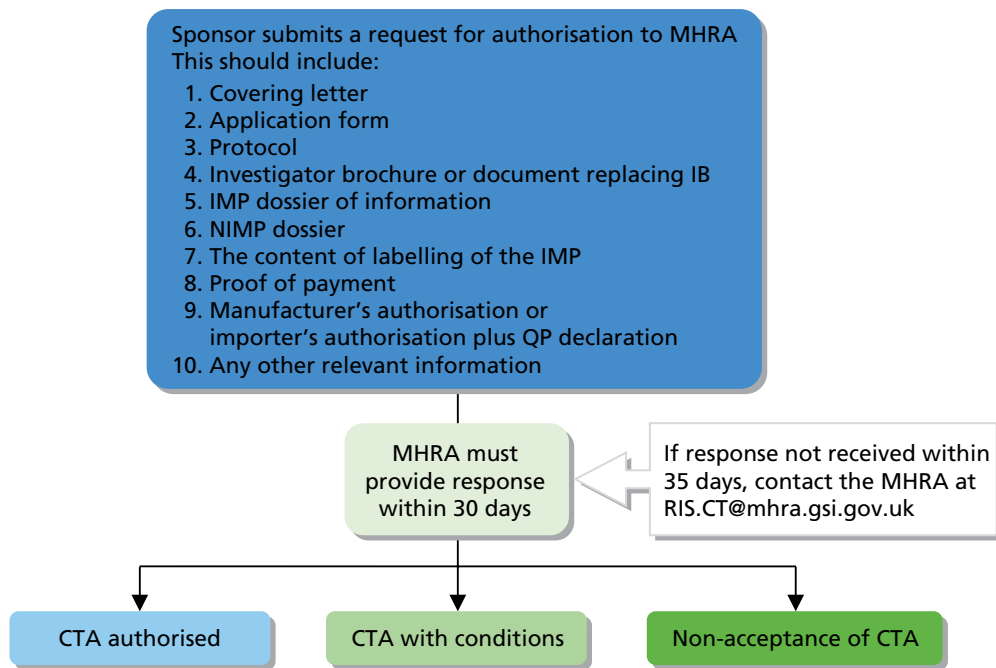


FIGURE 3 Obtaining a CTA.

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, details should 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. 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).

Patient Status and Tracking service

The PST (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, go to www.hscic.gov.uk/hes.

Devolved Nations data linkage services

Scotland (see ISD Scotland at www.isdscotland.org), Wales (see Health Information Research Unit Secure Anonymised Information Linkage Databank, or SAIL: www.adls.ac.uk/secure-anonymised-information-linkage-databank) and Northern Ireland all have independent registries that offer medical record linkage services.

Section 4 Trial planning and development

Managing a trial is the same as managing any other project or business, for example a new house build, or a new import and export business. Good project/trial management skills are an essential part of a Trial Manager's role. There are numerous online project management resources available. These include tools for developing project plans and timelines; evaluating risk and planning contingency; establishing clear processes; coordinating resources including staff; and monitoring progress and quality assurance. Software resources such as Microsoft Project may be helpful.

There are three aspects of a project that need to be successfully delivered, given in order of priority for a non-commercial trial:

- **Scope/quality:** this includes the number of participants recruited and the quality of the data recorded. This is usually the highest priority for a trial and needs to be controlled.
- **Budget:** any risks to the budget should be minimised. Funding supplements are hard to justify and should not be expected.
- **Timelines:** it may sometimes be necessary to extend the 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 in plenty of time.

For a commercial trial, timelines may be a higher priority than budget.

The following tasks contribute to the successful delivery of a trial:

- Maintaining good communications with all relevant parties.
- Determining the work required and developing a schedule with milestones, i.e. what needs to be achieved when. The critical path is the path of work that determines the duration and the path in which any delay will delay the entire trial. This should be the prime focus of attention during the management of the trial.
- Determining the resources required during the stages of the trial and the associated budget schedule. Note that maximum staff commitment to a trial should be 70–80% full-time equivalent (FTE) to allow for other commitments.
- Identifying and mitigating risks. 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/avoided by replanning.
 - Medium risks: contingency plans should be put in place for medium risks.
 - Minor risks (low likelihood and low impact) should be documented.
- 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. See below for more information on budget management. 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.ccf.nihr.ac.uk/Pages/RDSMap.aspx) 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.

Chief Investigators are also recommended to approach a CTU with expertise in coordinating multicentre trials, trial design, data management and analysis. Some funders expect a trial application to be developed in partnership with a suitably qualified unit. Information on the UKCRC-registered CTUs can be found via the UKCRC registered CTUs Resource Finder (www.ukcrc-ctu.org.uk/search/custom.asp?id=468).

Preparing the grant application

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

Applications to NIHR funding schemes typically have a brief 'outline' application followed, if successful, by a more detailed 'full' application. The full application is similar to a brief protocol, for example trial background, design, statistical considerations, data collection, team expertise and costs. As applications take considerable time to develop and collate, including CVs of co-applicants and costs, the days before the submission deadline can be very pressurised. Most funders have online application forms, but formal 'sign-off' by the Chief Investigator, and their head of department or institution, and 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, is usually required.

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) and members of the Association of Medical Research Charities (AMRC) can be adopted by the NIHR CRN portfolio and comprise of three cost types:

- **Research Costs:** costs attributed to the funder body for 'conducting' the research.
- **NHS 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 continued, for example appointments to obtain consent or in-patient stays for research purposes.
- **Treatment Costs:** covered by NHS commissioning arrangements and include care costs that would continue if the treatment/intervention continued in 'real care', for example drug/intervention costs, including administration and infusion time, or therapist time. The difference between standard treatment and the experimental treatment costs 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).

Further information on 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/DH_133882).

The AcoRD guidance supersedes earlier guidance contained in *Attributing Revenue Costs of non-commercial research in the NHS (ARCO)*. It 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. If your research was funded before the release of AcoRD, there are no changes to the funding arrangements.

Costing a research grant

First, you must check specific funder guidance regarding what costs can or cannot be included in the grant application and those of the organisation 'hosting' the research. For larger multicentre trials, a 'coordinating centre', typically a university or NHS trust, will hold the grant research 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 break the trial down into the time required for the main phases: 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, and the amount and type of data to be collected will influence staffing. A trial risk assessment should form part of grant application planning as it may impact on staffing requirements, for example for site visits or more frequent data reviews. In summary, identify all of the main trial tasks, who will be responsible for doing them and how long the tasks will take to complete. University staff may have access to Sirius web (www.siriusweb.leeds.ac.uk/offerSub.asp), which will calculate costs or within the NHS, the R&D department can provide similar support.

In England, industry-funded but academically led/-sponsored trials are not eligible to receive NHS support costs or treatment costs without adoption on the NIHR portfolio. Industry-sponsored studies operate at full cost recovery. More detailed information along with industry costing templates can be found at the NIHR Clinical Research Network Coordinating Centre website (www.crncc.nihr.ac.uk).

Trial/research budget checklist

- Salaries for trial staff including statisticians, health economists, qualitative researchers, the trial team.
- Randomisation system.
- Intervention: drug, placebo, packaging, distribution, equipment, and destruction.
- Laboratory or other reference tests.
- 'Flagging' of participant records if required for long-term trial follow-up with NHS Information Centre for health and social care (www.ic.nhs.uk).
- Computing: hardware, software, computer consumables and web design costs.
- Printing and postage costs: protocols, consent forms, data forms, questionnaires, posters and newsletters, questionnaire licence fees. Note: allow for postage cost increases over time and multiple mailings for non-responders. Utilise web distribution for newsletters to reduce costs if possible.
- 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/e-mail: to maintain regular contact with sites and participants, include voicemail if appropriate.

- Consumables: stationery including envelopes, office furniture, filing cabinets, photocopying, freepost licence for mailing questionnaires.
- Site costs: telephones, internet, photocopying, fax, data collection, nursing support staff and other site staff.
- Travel: site visits, launch and other investigator meetings, initiation and close-out meetings, staff training meetings, and researcher costs, possibly including accommodation and subsistence.
- IMP/intervention/device costs: manufacture/labelling/blinding.
- Meetings: trial management steering and monitoring groups and other meetings. Costs to consider include room hire, travel and refreshments. Consider opportunities to reduce the trial carbon footprint and reduce costs, such as teleconferencing/online meeting facilities.
- Publication and dissemination: protocol publication costs, mail shots to participants, journal publication fees and attendance at conferences.
- Archiving and storage: sufficient resources to allow archiving according to the appropriate regulations and to ensure publication of the final results. Note: GCP requires long-term commitment to trial data storage for 10 years.

Treatment and service support costs are trial specific. Compile a visit schedule and outline which tests or activities occur at each visit, such as screening, randomisation, treatment, and follow-up, test or procedure costs associated, number of tests and purpose to determine whether they are a treatment, service support or research. It is best to discuss service support costs with the CRN early on and similarly for treatment costs with the appropriate NHS trust's R&D department.

If the grant application is successful, funding is usually released upon contract signature or an agreed date post signature. This may take 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 budget spend.

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. 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 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.

INVOLVE is a national advisory body funded by the NIHR to support public involvement in NHS, public health and social care research. More information, guidance and practical tips are available from the 'Resources for Researchers' section of the INVOLVE website (www.invo.org.uk).

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.
- 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. See INVOLVE resource for researchers at www.invo.org.uk/resource-centre/resource-for-researchers.
- 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 an extremely 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 feel they are often consulted, without seeing any change as a result.

'Briefing notes for researchers: public involvement in NHS, public health and social care research' and 'Public Involvement in clinical trials: Supplement to the Briefing Notes for Researchers' (www.invo.org.uk/posttypepublication/public-involvement-in-clinical-trials/) provide useful advice and examples for researchers who design and conduct trials.

4.3 Risk assessment

The purpose of risk assessment is to identify the potential hazards associated with the trial, to assess the likelihood of those hazards occurring and resulting in harm, and to inform the development of relevant risk-mitigation plans along with proportionate trial management and monitoring plans.

It is recommended that a risk assessment be undertaken at an early stage in the development of a protocol, and revisited periodically over the lifetime of a trial to take into account new information and issues as they develop. Ideally, the first risk assessment should be prior to submission of a funding application so that appropriate operational resource requirements are considered and requested.

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:³²

- 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 that 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 IMP trials, the IMP risk category and safety-monitoring plan may be submitted to the MHRA with the CTA to ensure that there is shared understanding on this key aspect of the trial.³²

Active sponsor and trial team oversight and regular review of the risk assessment during the course of the trial is 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.³²

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. The protocol will be read by many different readers – 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).

Note that clear writing and an easily navigated structure are the cornerstones of a good protocol.

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 to divide sections.
- A protocol for a CTIMP may be very different in size and scale to a small observational study – it has to be appropriate and proportional. See 2.5 Protocol, 2010/C 82/01 at www.meduni-graz.at/ethikkommission/Forum/Download/Files/CT_1.pdf.
- Ensure that it has a structure that is logical and flows, and that items follow through the different sections, for example that the objectives appear in the statistical analysis plan. 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.
- Portrayal 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 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 with a good protocol, use that as a template. Many sponsors have protocol templates available as a starting point.
- 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 trial protocol can be submitted for publication. The protocol should ideally be submitted at the start of the trial, but protocols will usually be accepted up to 1 year after the end of participant recruitment, for example to *Trials* journal.

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.

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 of any publications arising from their funding.

Authorship

Overall arrangements for authorship should be described in the protocol/publication policy. Many large trials have group authorship, with a list of contributors giving details of who did what, for example Trial Steering Group, collaborating investigators, and acknowledging participants and the TSC.

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.

External systems include central telephone randomisation, web-based systems, e-mail or fax to the coordinating centre and automated electronic systems with voicemail recognition. An automated electronic system with voicemail 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 the allocation can be subverted if an investigator wants the next allocation for a participant. There is no central record that the allocation has been taken and abandoned without the site being monitored regularly or data 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: a Trial Management Group (TMG), a Trial Steering Committee (TSC) and a 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(s), Trial Manager, Statistician and Data Manager. 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 oversight of the trial on behalf of the sponsor and funder, and 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 new information regarding the intervention or clinical area that may 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 data emerging from the trial, 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 participants 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.doc.

It is expected that nearly all randomised controlled trials (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 to coincide with TSC meetings and allow for reports to be shared.

4.7 Regular reporting

At the outset of the trial, 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.

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 body you are required to report to. It is likely to include progress reports and recruitment data, and an end-of-trial report.

- How often are reports required and in what format? Ensure you know what the timing and frequency of each report type are and in what format the report should be submitted, 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?
- 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.
- Financial reporting: consider when, what and to whom you need to report the status of the trial finances. Obviously, regular reports to the Chief Investigator during management group meetings will be necessary, and maybe 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.
- If your CTU is responsible for a portfolio of trials:
 - try to sequence meetings, especially of DMC, so that the reports are not all due at the same time. The project plan should include the deadline dates for all scheduled reports.
 - produce templates that can be used for more than one.

Section 5 Trial set-up

Trial set-up is a very busy time as there are many issues to consider and several steps to undertake.

At this stage of the plan the operational elements of the trial need to be considered and finalised. Please note that processes described below can be carried out in parallel.

5.1 Trial coordinating centre

What is a trial coordinating centre?

The trial coordinating centre is 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 and sponsor to determine delegated tasks.
- space, staff and equipment.
- systems for data management, administration, finance, personnel management.
- The contract with the host institution, who may be the sponsor as well, should provide adequate space and accommodation.
- Remember that 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:

- Chief Investigator(s)
- Trial Manager
- Programmer/IT support
- Database Manager and/or Data Clerks
- Trial Statistician.

The trial team is customised to meet the needs of the trial, which may evolve over time. You may need more of one skill and less of another, for example two Data Clerks and 0.5 of a Programmer. Begin to draw up a blueprint of how the team will function and what the members' responsibilities will be, and anticipate workload hot spots.

5.2 The trial team

Chief Investigator

The Chief Investigator 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 who commands the respect of fellow investigators and the trial team. The Chief Investigator 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 Chief Investigator takes overall responsibility for the whole trial, they do not have to be involved

in the day-to-day management. If the trial is multicentre, each site will have a Principal Investigator who takes the lead for activities at their site.

Trial Manager

One of the keys to success is trial management. The Trial Manager, therefore, holds a pivotal position. Successful Trial Managers need to be multitalented, hard working, well organised, capable planners and excellent communicators. Never underestimate the importance of common sense and attention to detail.

Programmer

Programmers with specific experience in trials are rare. The ability to work with the Trial Manager and understand the requirements of the trial is essential. They will need knowledge of RCTs and an in-depth knowledge of the specific trial being conducted. They should be able to use their knowledge in an innovative way, and a willingness to learn is essential. A Programmer will be needed throughout the trial to develop, establish and maintain the programs. Programming includes not only programs for data management and analyses but general monitoring systems for all aspects of the trial. If commercial software is used, less programming/IT support may be required.

Database Manager

The Database Manager will have an intimate knowledge of the trial's data collection and management systems.

Data Assistant

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

Statistician

A trial will rarely need full-time statistical support. Input is concentrated around the planning phase, monitoring the 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 produced.

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 Equipment

Get advice on hardware and software before making purchases; talk to the experts; and talk to other trial teams.

Remember: technology changes rapidly – has the budget got sufficient funds 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, answerphones, laptop computers, mobile phones, pagers, scanners, dedicated internal computer network and laboratory equipment.
- 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.

5.4 Trial identity and marketing

The trial should be promoted to ensure that it is at the forefront of investigators and participants minds.

Consider the following

- Aim to give the trial an individual identity.
- The name, acronym and logo should make it recognisable and memorable.
- Consult the relevant experts, such as medical illustration, departmental reprographics.
- Promote the trial identity – make it known – always use it and publicise it.
- Use the trial identity on all customised stationery, data forms and other promotional materials.
- Set up dedicated telephone lines, answering machines, fax machines, e-mail addresses and website addresses.

Promotion and marketing of the trial, as outlined above, are vital components of the overall trial management plan.

Managing the trial as a business

Serious thought should be given to how the trial will reach the widest relevant audience and be inclusive. Consider treating the trial as a business by adopting methodologies and management techniques from the business world. Francis *et al.*³⁴ suggested that dimensions of running a successful trial include 'marketing', 'sales' and 'on-going client management', and developed a reference model from marketing theory.

5.5 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, 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. 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).

Examples include:

- protocol content and format
- document version control
- setting up and maintaining a Trial Master File (TMF)
- design and development of Case Record/Report Forms (CRFs)
- database design
- archiving of essential documents
- managing and reporting adverse events
- monitoring and source data verification
- drug pack (intervention) management systems if needed.

A number of organisations provide example SOPs on their websites and many CTUs have core SOPs to follow.

5.6 Document development and design

To ensure that people will understand clearly what the trial is about and what it entails, all documentation, including items such as the protocol, participant information leaflet, questionnaire information for GPs, should be written in a clear, unambiguous way. Scientific terms are unlikely to be understood by participants and must be clearly explained.

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.
- Change long phrases to shorter ones.
- Pilot your information on the people it is planned for and revise using the feedback obtained.
- Think about relevance to the audience or specific requirements. For example; short versions for use in emergency situations, large print for those with sight issues or the elderly. Also consider other communication styles such as audio recording, simple language and pictures for young children.

Data collection forms

The logic described above is also applicable to the data collection forms or CRFs these are required in order to collect data necessary to monitor participant progress and safety and, ultimately, for analysis of the trial end points.

Forms can be paper or computer based and there are some important points to note in developing them.

- Multiple-choice questions: on paper it is straightforward to list a number of options and say 'tick one box only'. When transcribing this to a computer system the usual method is to use a series of 'radio buttons', where only one can be selected; the alternative is a drop-down list to select from. 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.
- 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 the other options. The preferred solution for computer systems is to have a drop-down list of four options: 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. Blank answers should never be accepted.
- Drop-down lists: these are much easier to manage on a computer system than on a paper form, especially where there are a lot of options to choose from. They also rule out the possibility of spelling errors.
- Text input: free text is always problematic, especially when being transcribed from paper to computer.
- Some paper forms use individual boxes for each character to try to force clarity, especially for names and addresses.
- Using a coding frame to code free text as the data accumulate will make it usable at the analysis stage.
- When using free-text fields in a computer system, include an automated spell-checker – but make sure that it includes all necessary medical terms and names of medications.

5.7 Trial Master File/Investigator's Site File

A TMF containing essential documents 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 principal site. 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 and version date.

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 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:

- 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
 - sample CRF
- documents relating to participants in a trial
 - recruitment procedure, for example recruitment advert if used
 - consent form(s) used
 - participant information leaflet(s) used
 - any other information given to participants, for example questionnaires
- agreements between involved parties
 - for example, signed agreement between the sponsor and the trial site detailing responsibilities and financial 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
 - letter of indemnity (non-NHS sponsors only)
 - funding arrangements, 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
- evidence that all trial staff are qualified and authorised to work on a trial
 - for example CVs, honorary contracts
 - record of training in trial procedures, including GCP
 - delegation of responsibilities log
- information on any laboratory or technical tests to be performed, for example normal ranges, accreditation of facilities
- detail regarding the specific intervention(s) such as IMP information for a CTIMP
 - Investigator’s Brochure
 - labelling, certificate of analysis (TMF only)
 - 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.

5.8 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 sending of appointment letters, importing of laboratory results.

All systems require *validation*; that is, it can be demonstrated that a system is working as specified, and reliably so. System validation is regarded as both good practice and an essential regulatory requirement. The burden of validation can be significant.

Computer systems

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*, 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 always be kept as simple as possible. Designing the screen to match the paper form greatly enhances the quality of data input.
- Try to 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.
- Have 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 restrict 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).

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 are 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 once only 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.

System security is vital. All users must be given a unique username and password 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 www.ukcrc.org/infrastructure/ctu/activitiesassociatedwithctu.

5.9 Investigator/site selection

Investigator/site selection is crucial to the success of the trial. Selecting investigators who have a known track record in conducting trials is the first step. However, investigators 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; check CV, health professional registration, GCP certificate, research experience, specialist knowledge
- have suitable facilities including pharmacy if IMP storage is required, 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 investigator to conduct the trial safely and properly.

Site initiation visit/Investigators' meeting

Before the 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 planning and key dates. This includes 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.

5.10 Checklist – before recruitment starts

Before recruitment starts, ensure that all trial sites have all the information they require and that full written guidance is provided.

- Ensure that the local team is trained in trial procedures. 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 the key people from the site and harness their experience and expertise. Involving the clinical team and gaining their support will aid recruitment.
- Agree trial logistics locally and ways of optimising recruitment at the site.
- Inform all sites that REC, NHS R&D approvals and CTA, for CTIMPs have been given.
- Circulate approved site list.
- Ensure all sites have the correct versions of documentation and copies of relevant approval letters.
- Ensure that all contracts/site agreements are in place.
- Inform all sites who the sponsor(s) are, and of any allocated or delegated duties.
- Confirm monetary agreements.
- Ensure all sites know the process for safety reporting/pharmacovigilance.
- Inform all sites they can begin recruiting when initiation visit/appropriate training is completed.

5.11 Managing the budget

Practically all trials will have been costed using 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 or 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.

Research costs include staff salaries, materials and equipment, expenses such as travel, and payments to contractors/collaborators. A budget schedule should be developed based on how and when the money is to be spent. 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:

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

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 see 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.

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 to always 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: 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.

Assess the trial processes for cost savings 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.
- 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 hand-matched at a later date.
- Consider using teleconferences or Skype™ 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 of 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.

5.12 International trials

Trials that involve international collaboration must comply with national and local requirements. Some specific areas to consider when planning international involvement are:

- local language translations
- indemnity arrangements
- ethics approvals
- local permissions
- contracts/agreements
- public involvement
- data management
- data protection
- units of measurement.

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
- record of any protocol violations or deviations
- records for any new staff
- records of correspondence/meetings with sites
- monitoring visit reports
- signed consent forms, site file only – or may be collected centrally
- source documents, site file only
- signed, dated and completed CRFs and corrections
- safety reports
- annual progress reports including REC, MHRA
- subject screening log
- subject ID code list, site file only
- IMP accountability
- records of any tissue samples collected.

6.2 Trial recruitment

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

- where participants are recruited
- who will recruit them
- 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 visit or over the telephone 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 down the line. Provide clear written instructions for team members to refer to. 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. 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
 - e-mail
 - publication and letters
 - website
 - newsletters
 - personal contact
 - Skype™.

Ideas to consider to ensure optimal recruitment

- Contact relevant voluntary organisations and other patients groups for advice on how to raise awareness.
- 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'.

Monitoring recruitment targets

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

- set realistic targets for both numbers of participants and numbers of centres – review regularly
- use computer systems to monitor 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
- 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 incentives, mugs, post-its, pens, mouse mats, key-rings, and trial-specific items have proved useful. It should be noted that NIHR funding should not be used to support such merchandise and the NIHR does not support the provision of promotional materials.
- Attend conferences with trial-specific literature; take an exhibition stand.
- Recruitment prizes, for example prize draws for reaching a milestone, for example the 100th patient, all help to maintain interest and motivation for the trial.
- E-mail 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.
- Consider adding more centres if recruitment rates are lower than anticipated.

Encourage ownership by investigators

- Publish regularly 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 e-mails.
- Discuss 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?
- Does the eligibility criteria need reviewing?
- Are investigators still interested?
- Are participants prepared to join?
- Are procedures appropriate and flexible?

6.3 Retention and follow-up

- Consider the aims of the trial, the population under investigation and the resources available.
- Make sure you have all the necessary permissions, such as Ethics, NHS Health and Social Care Information Centre, NHS Personal Demographics Service.
- Make sure you have the necessary consent and contact details so you can follow-up participants.
- 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. Consider sending each site a report listing due dates of follow-up.

Other ideas that have proved successful in previous trials include:

- notifying the participant by letter when contact is due
- 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
- 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
- NHS IC, HES, 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
- focus 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 2009³⁵ 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 e-mails more personal and keeping them short; offering incentives. (see <http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000008.pub4/abstract;jsessionid=D8D0A6A1B664A489E06AEBF6FBBCF92F.d03t04.>)

6.4 Data collection and management

Consistency in data collection is important to increase ease of response and precision. Missing data are a major threat to the analysis. Therefore, it is important that additional effort and energies are expended in ensuring low levels of missing primary outcome data. This can be done through several means and depends on how data are being collected, for example training and use of dedicated data collectors.

The success or failure of any trial rests on the accuracy and validity of the data.

Accuracy depends on a number of factors: the reliability and calibration of the instruments used to take readings; the training, accuracy and reliability of the data entry clerks; the legibility of handwriting; and transcription errors when copying data or records. 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; and preventing the opportunity to falsify data.

Data entry checking and validation

The use of computer systems for recording and analysing data presents more opportunities for data entry errors as more people with less expertise could be involved with entering the data. However it also provides more capability to identify and query out-of-range or invalid data at the point of entry. The key to the process is to 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, and calculate derived values from raw data in the system.

The use of internet-based data management systems facilitates contemporaneous and expedient data monitoring, which means that incorrect or ambiguous data can be corrected promptly, and improves data quality. Real-time data entry means that the Trial Manager can see an overview of activity in all centres. Most clinical data have 'normal' ranges and some systems will query or reject data outside these ranges. It is important that the system has ranges that reflect the population being studied. There are instances when individual values may be possible but when combined create a derived value that is definitely impossible, so some comparative logic needs to be applied.

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 – but what if the data were recorded incorrectly in the first place? 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.

Computer systems can be coded 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.

Source data

The MHRA and trial sponsors require 'source data' to be available for inspection and audit during and after the trial, but the definition and meaning of this is not always clear. One definition is where the data are first recorded or written down – this is fine for paper records but what happens where data are input directly into a computer system? What if a patient is responding to a questionnaire over the telephone, and the operator enters the answers directly into a computer system? Is the source data the computer record – or should it be a recording of the telephone call?

When using instruments to take measurements, and following this logic, the source data are the values produced by the instrument that takes the reading or performs the analysis. These may be input directly into a computer system, or written down on a paper form and then transcribed. Direct input has only one opportunity for a transcription error; writing information down and then input to a computer system has two opportunities.

In the past, paper CRFs were always regarded as the essential source data and a set of rules were formulated as to how these should be handled, which have become increasingly complex.

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), is 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.

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 ethics committee and registered under the Data Protection Act 1998.⁴
- Ensure adequate security and restricted access to paper records by use of lockable cabinets.
- Ensure adequate security and restricted access to electronic records by use of password-protected systems on a secure network.

- 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 e-mail addresses.
- Use a daily back-up – stored off-site.
- 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 available
- the trial is conducted in compliance with the protocol, SOPs, 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. Further considerations that may influence the risk and monitoring are the objectives, purpose, design, complexity, blinding, size and end points 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. remote, central, 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) and the MHRA Risk Adaptation in Clinical Trials webpage (www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/News/CON126145).

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
- 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 and accountability
- 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 end point data
- central statistical monitoring to identify unusual data patterns that may require further investigation and verification of data against external sources.³⁶

If a site monitoring visit is performed, a report should be written summarising what was reviewed, findings and actions, and filed 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
- 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 the 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.

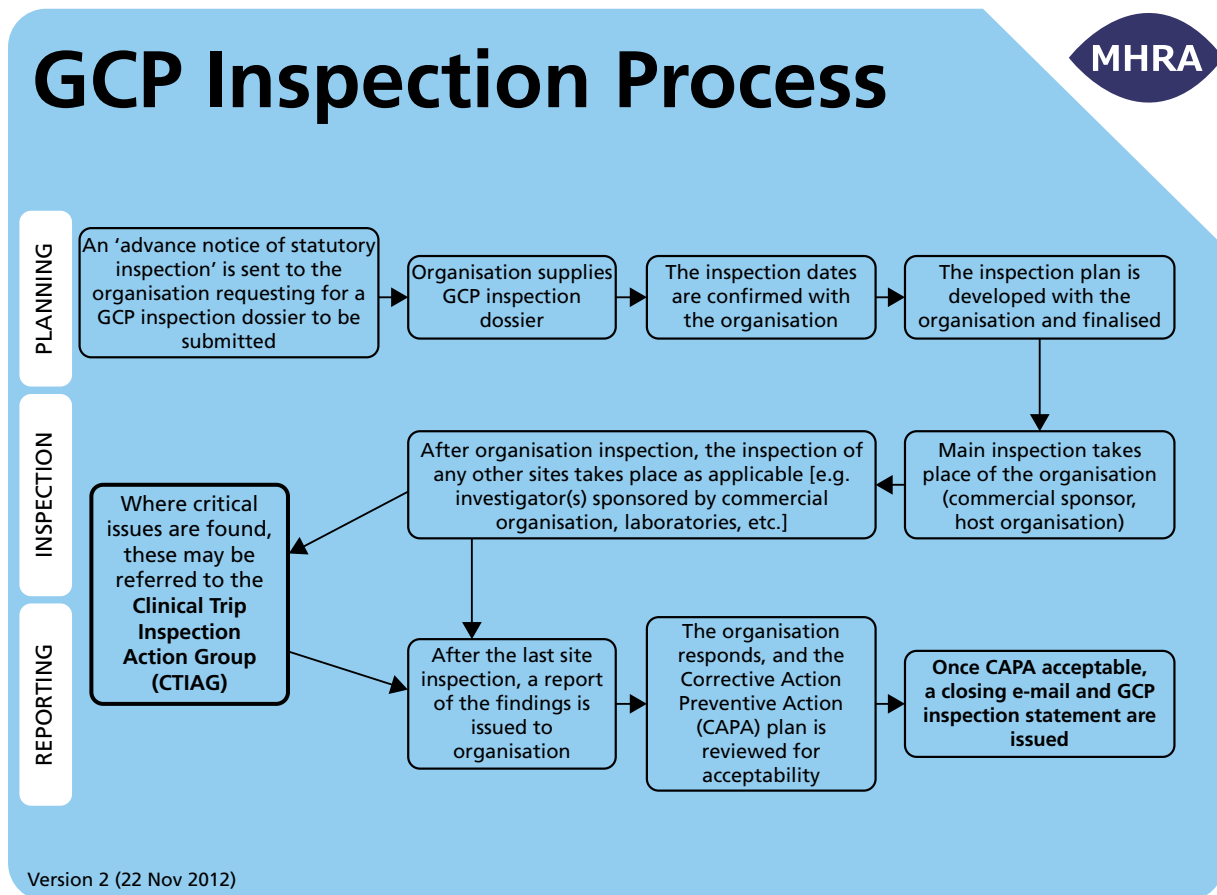
Notification of a routine inspection

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.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con009394.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.
- Inspectors may require access to the database if electronic data capture is performed, or they 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. Prepare a summary document or tracking log detailing initial approvals and subsequent protocol/informed consent form amendments. Include submission and approval dates, reasons for amendments and their current status.
- 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 inspectors 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 within a finite time to respond to the inspectors’ report including timelines and proposed changes.

Further information about the MHRA inspection process is available from the MHRA website at www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Theinspectionprocess/index.htm.

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 all 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.
- 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 drug is being exported to the 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 an anaphylactic reaction. 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
 - at the request of the DMC
 - during any unmasked 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.
- 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 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 are 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 into design, conduct and troubleshooting. 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 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 the Trial Pharmacists should be included in the trial protocol and SOPs. In addition, a Pharmacy Trial File should contain all relevant information specific to a trial, including code-breaking/unblinding procedures.

International trials will also have local pharmacy regulations to follow. It is essential that a pharmacy SOP is in place for each international site outlining the pharmacy procedures for the duration of the trial. It is advisable to consult the relevant competent authorities or regulatory authorities to obtain more detail regarding specific requirements.

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
- including 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 10.³⁷

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

The regulations allow trial protocols to specify SAE that do not require immediate, expedited, reporting by site investigators, for example 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.

Further information about definitions and reporting requirements of adverse events can be found at the HRA website (www.hra.nhs.uk).

Section 7 Trial closure

Final trial closure occurs once all data are received, analysed and ready to be reported. Depending upon the length of follow-up, this can be a long time after the trial closes to recruitment.

A definition for the end of the trial, and the planned trial end date, should be specified in the protocol, the NRES application, NHS R&D applications/NHS permissions and MHRA application where relevant, and will have been notified to the sponsor and the funder.

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 End of the recruitment period

Trial recruitment will close:

- when the recruitment target, as defined in the protocol, has been reached
- if the DMC recommends that the trial should close and the TSC endorses this decision
- if, in the absence of a DMC, the TSC decides to close recruitment.

7.2 Financial closure

When the trial closes to recruitment, the Trial Manager should ensure that all recruitment payments to centres have been made. Reimbursement may also be made after the follow-up period on return of clean and complete CRF data.

7.3 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 sent a letter outlining their ongoing obligations to the trial.

7.4 Extension to trial closure

To extend a trial beyond the agreed closure date, you will 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 closure 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 final end date is extended, then NRES must be notified using a substantial amendment form for approval of this change. All investigators, R&D departments, the sponsor and, if relevant, the MHRA should also be notified.

7.5 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 using the end-of-trial form within days of closure.

The sponsor should be notified immediately by letter or fax.

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

7.6 Planned closure

Informing investigators

Investigators should be informed of trial closure via a letter from the Trial Manager or the Chief Investigator. This letter should:

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

7.7 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.

Final close-out of the trial can only be done once the TMF and site files are confirmed as complete.

The investigators are responsible for informing local personnel at their centres that the trial has closed.

7.8 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 centres/pharmacies are aware of the requirements for the end of trial and that proof of destruction is received by the coordinating centre in a timely manner.

For trials conducted within the EU, the competent authority in each member state should be informed of the end of the trial. A form should be completed on EudraCT that lists:³⁸

- number of participants recruited, withdrawn, completed and drop-outs
- SUSARs, including a critical appraisal of these reactions
- anticipated date of final data analysis and of final report availability.

The EudraCT declaration of end of trial form should be completed.

7.9 Informing participants

Participants should be informed of the trial closure where possible. This should be discussed and agreed by the TSC and any personal communication approved by the REC.

7.10 Informing the sponsor

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

7.11 Informing the Health Research Authority

The Trial Manager should, on behalf of the Chief Investigator, inform the HRA that a trial has reached its defined end date using the end-of-trial form within 90 days of closure.

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 and the REC.

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. Most NIHR funded trials are required to submit a report for publication in the NIHR Journals Library (www.journalslibrary.nihr.ac.uk/). Attention is needed 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 within 12 months 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, and MHRA if relevant, 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.

Participants should be informed of the trial results. This could be via a letter, an easy-to-understand summary on the trial website, or newsletters to participating centres, for example GP practices, patient groups, or hospital outpatient departments.

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 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. Copy should be submitted to the funder prior to submission, taking into account the funders' timescale for review. Funders must be appropriately acknowledged with the use of a logo and/or statement of support as appropriate in all outputs.

Prior to signing any journal copyright 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.

Consider also publishing in formats and media accessible to trial participants such as websites or patient newsletters.

The Department of Health (England) and the NIHR require that, for funding applications submitted after 1 April 2007, electronic copies of any research papers that have been accepted for publication in a peer-reviewed journal or final reports and/or executive summaries, which are supported in whole or in part by Department of Health or NIHR funding, are deposited at the earliest opportunity – and in any case within 6 months – in Europe PubMed Central (<http://europepmc.org>) (see Department of Health/NIHR-funded research and Europe PubMed Central at www.nihr.ac.uk/research/Pages/Research_Open_Access_Policy_Statement.aspx).

Authorship

Arrangements for authorship will 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).

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. It may be possible to apply to present your results outside of the formal call for abstracts.

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 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 documents should be filed in an organised way in the TMF. This will facilitate trial management, audit and inspection.

The TMF should be set up at the beginning of a trial and maintained throughout. Archiving applies to both the investigator sites and 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 for at least 5 years after the conclusion of the trial (see Directive 415 2005/28/EC Article 17 for further detail for CTIMPs¹⁰), or longer for trials supporting marketing authorisations (EU Directive 2003/63/EC³⁹), or as per national legislation. If in doubt, discuss archiving with the funder and sponsor and review any appropriate legislation.

Documents should be maintained in a legible condition. Prompt retrieval should be possible. Plans for archiving trial documents should be made in the planning and development phase of a trial and costs of storage should be considered. Adequate and suitable space should be provided for the secure storage of all essential records upon trial completion. The facilities should be secure, with appropriate environmental controls and adequate protection from fire, flood and unauthorised access. The storage of the sponsor's documentation may be transferred to a subcontractor, such as a commercial archive, but the ultimate responsibility for the quality, integrity, confidentiality and retrievability of the documents resides with the sponsor or delegated person. This means that the sponsor or delegated person should audit the site and be satisfied, and document, that the storage is appropriate. Appropriate contractual agreements transferring responsibilities under the Data Protection Act 1998⁴ should be signed.

An archive index/log should be maintained to record all essential documents that have been entered into the archive, and to track and retrieve documents on loan from the archive.

The investigator should make the sponsor aware of the arrangements for the documents to be stored at investigator sites. If the investigator becomes unable to store their essential documents, the sponsor should be notified in writing so that alternative storage arrangements can be agreed. If the investigator is no longer able to maintain custody of their essential documents, the sponsor should be notified in writing and the investigator/institution should see to it that appropriate arrangements can be made.

Storage of personal data are subject to applicable elements of EU Directive 95/46/EC⁴⁰ and the Data Protection Act 1998.⁴

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 security measures must be taken with electronic data, particularly with identifiable or link-anonymised data. Appropriate back-up of electronic data must be considered to mitigate against the risk of failure of storage media.

Access to archives should be restricted to authorised personnel. Any change the ownership and location should be documented in order to allow tracking.

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.

References

1. Pocock SJ. *Clinical Trials: A Practical Approach*. Chichester: Wiley; 1983.
2. European Parliament and Council. *EU Commission Directive (2005/28/EC)*. 2005. URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>. Accessed 31 October 2013.
3. Department of Health. *Research governance framework for health and social care*. 2nd edn. London: Department of Health; 2005. URL: <https://www.gov.uk/government/publications/research-governance-framework-for-health-and-social-care-second-edition>. Accessed 31 October 2013.
4. Great Britain. *Data Protection Act 1998*. London: The Stationery Office; 1998.
5. Great Britain. *Freedom of Information Act 2000*. London: The Stationery Office; 2000.
6. Great Britain. *Mental Capacity Act 2005*. London: The Stationery Office; 2005.
7. Great Britain. *Human Tissue Act 2004*. London: The Stationery Office; 2004.
8. Great Britain. *The Medicines for Human Use (Clinical Trials) Regulations 2004*. London: The Stationery Office; 2004.
9. Great Britain. *The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006*. London: The Stationery Office; 2006.
10. Great Britain. *The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006*. London: The Stationery Office; 2006.
11. Great Britain. *The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008*. London: The Stationery Office; 2008.
12. Great Britain. *The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009*. London: The Stationery Office; 2009.
13. Great Britain. *The Medical Devices Regulations 2002*. London: The Stationery Office; 2002.
14. Great Britain. *The Medical Devices (Amendment) Regulations 2003*. London: The Stationery Office; 2003.
15. International Conference on Harmonisation (ICH). *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1)*. 1996. URL: www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html. Accessed 31 October 2013.
16. Great Britain. *Adults with Incapacity (Scotland) Act 2000*. London: The Stationery Office; 2000.
17. Great Britain. *Human Tissue (Scotland) Act 2006*. London: The Stationery Office; 2006.
18. European Union. *Clinical Trials Directive (Directive 2001/20/EC)*. 2001. URL: www.eortc.be/services/doc/clinical-eu-directive-04-april-01.pdf. Accessed 31 October 2013.
19. Great Britain. *The Medicines Act 1968*. London: The Stationery Office; 1968.
20. Great Britain. *The Medicines (Marketing Authorisation and Miscellaneous Amendments) Regulations 2004*. London: The Stationery Office; 2004.
21. Great Britain. *The Medicines (Advisory Bodies) Regulations 2005*. London: The Stationery Office; 2005.
22. European Commission. *Directive 90/385/EEC*. 1990. URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1990L0385:20071011:en:PDF>. Accessed 31 October 2013.

23. European Commission. *Directive 93/42/EEC*. 1993. URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF>. Accessed 31 October 2013.
24. European Parliament and Council. *Directive 98/79/EC*. 1998. URL: <http://ec.europa.eu/enterprise/policies/european-standards/harmonised-standards/iv-diagnostic-medical-devices>. Accessed 31 October 2013.
25. European Parliament and Council. *Directive 2007/47/EC*. 2007. URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:247:0021:0055:en:PDF>. Accessed 31 October 2013.
26. Great Britain. *The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010*. London: The Stationery Office; 2010.
27. Great Britain. *The Medical Devices (Amendment) Regulations 2007*. London: The Stationery Office; 2007.
28. Great Britain. *The Medical Devices (Amendment) Regulations 2008*. London: The Stationery Office; 2008.
29. Great Britain. *The Medical Devices (Amendment) Regulations 2012*. London: The Stationery Office; 2012.
30. Califf RM. Clinical trials bureaucracy: unintended consequences of well-intentioned policy. *Clin Trials* 2007;**6**:496–502.
31. Hearn J, Sullivan R. The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK. *Eur J Can* 2007;**43**:8–13. <http://dx.doi.org/10.1016/j.ejca.2006.09.016>. Accessed 31 October 2013.
32. MRC/DH/MHRA joint project. *The Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products*. URL: www.mhra.gov.uk/home/groups/l-ctu/documents/websitesresources/con111784.pdf. Accessed 31 October 2013.
33. International Organization for Standardization (ISO). *Clinical investigation of medical devices for human subjects – good clinical practice (ISO 14155:2011)*. Geneva: ISO; 2011.
34. Francis D, Roberts I, Elbourne DR, Shakur H, Knight RC, Garcia J. Marketing and clinical trials: a case study. *Trials* 2007;**8**:37. URL: www.trialsjournal.com/content/8/1/37. Accessed 31 October 2013.
35. Edwards PJ, Roberts I, Clarke MJ, DiGuseppi C, Wentz R, Kwan I, et al. Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev* 2009;**3**:MR000008.
36. Buyse M, George SL, Evans S, Geller NL, Ranstam J, Scherrer B, et al. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Stat Med* 1999;**18**:3435–51. [http://dx.doi.org/10.1002/\(SICI\)1097-0258\(19991230\)18:24<3435::AID-SIM365>3.0.CO;2-O](http://dx.doi.org/10.1002/(SICI)1097-0258(19991230)18:24<3435::AID-SIM365>3.0.CO;2-O). Accessed 31 October 2013.
37. European Parliament and Council. *EudraLex volume 10: clinical trials guidelines*. Brussels: EudraLex; 2013. URL: <http://ec.europa.eu/health/documents/eudralex/vol-10/>. Accessed 31 October 2013.
38. EudraCT. *Community clinical trial system*. London: EudraCT; 2013. URL: <https://eudract.ema.europa.eu>. Accessed 31 October 2013.
39. European Parliament and Council. *Directive 2003/63/EC*. 2003. URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:159:0046:0094:en:PDF>. Accessed 31 October 2013.
40. European Parliament and Council. *Directive 95/46/EC*. 1995. URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML>. Accessed 31 October 2013.