



The Guide to Efficient Trial Management

Effectively managing clinical trials

The Sixth Edition (2018) of the Guide to Efficient Trial Management was produced by an appointed Editorial Board and a panel of reviewers all of whom are trial managers, or who have relevant expertise, on behalf of the UK Trial Managers' Network.

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- Barbara Farrell:** Former Trial Director, Honorary Research Fellow, National Perinatal Epidemiology Unit, University of Oxford.
- Shelley Rhodes:** Deputy Chairperson of the editorial board and Senior Trial Manager & Exeter Clinical Trials Support Network Manager, Exeter CTU.
- Sam Barratt:** Trial Manager, MRC CTU at UCL.
- Alison Evans:** Regulatory Manager, Advanced Therapy Trials, UCL.
- Kirsteen Goodman:** Trial Manager, NMAHP Research Unit, Glasgow Caledonian University.
- Zoe Gray:** Director of INVOLVE Coordinating Centre.
- Lynda Harper:** Clinical Project Manager, MRC CTU at UCL.
- Suzanne Hartley:** Head of Trial management – Complex Interventions Division, CTRU, University of Leeds.
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Please note that guidance can change, so please use the relevant links to ensure you have the most up-to-date information.

Devolved nations

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

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 Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA), before and during trials.

Commonly used terms and acronyms

AcoRD Attributing the costs of health and social care Research and Development. Guidance that provides a framework for the NHS and its partners to identify, recover and attribute the costs of health and social care research and development.

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

Amendment A written description of a change or formal clarification. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial and to advise which review bodies the amendment should be submitted to.

ATMP Advanced Therapy Medical Products.

ATIMP Advanced Therapy Investigational Medicinal Products.

CAG Confidentiality Advisory Group.

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

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

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

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

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

Common European Submission Portal (CESP) CTA submissions must be processed through the CESP which provides a simple and secure mechanism for exchange of information between applicants.

CONSORT Consolidated Standards of Reporting Trials. An evidence-based, minimum set of recommendations for reporting randomised controlled trials. Extensions of CONSORT exists for non-inferiority, equivalence, cluster designs, non-drug treatments, herbal interventions, patient reported outcomes.

CTIMP Clinical Trial of an Investigational Medicinal Product.

Designated Individual (DI) Activities under the Human Tissue Act, require a license and the license holder also has a Designated Individual (DI) who has a set of specific legal responsibilities for compliance with the Human Tissue Act.

DMC Data Monitoring Committee. A DMC is an independent group of experts who monitor patient safety and treatment efficacy data, while a clinical trial is ongoing.

DPA The Data Protection Act 2018 makes our data protection laws fit for the digital age when an ever increasing amount of data is being processed; empowers people to take control of their data; supports UK businesses and organisations through this change; ensures that the UK is prepared for the future after we have left the EU.

DSUR Development Safety Update Report. This is the annual safety report required for CTIMPs.

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

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

GDPR General Data Protection Regulation. The EU General Data Protection Regulation (GDPR) replaces the Data Protection Directive 95/46/EC and was designed to harmonize data privacy laws across Europe, to protect and empower all EU citizens' data privacy and to reshape the way organisations across the region approach data privacy.

Good Clinical Practice (GCP) A set of ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Some trials are governed by regulatory requirements such as CTIMP, ATIMP, Medical Devices, IRMER etc.

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 gene therapy medicinal product; usually no REC approval is required.

GMO Genetically Modified Organism.

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.

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

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

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

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

Investigational Medicinal Product (IMP) A medicine/foodstuff/placebo, as defined by the regulations, used within a clinical trial.

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

Investigator Brochure A compilation of clinical and pre-clinical pharmacological/biological data relevant to the use of that IMP(s) in human subjects.

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

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

IP Intellectual Property.

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

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

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

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

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

Multisite 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, fund, maintain and manage the research, research staff and infrastructure of the NHS in England. The mission of the NIHR is to maintain a health research system in which the NHS supports outstanding individuals, working in world-class facilities, conducting leading-edge research focused on the needs of patients and the public.

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

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

NHS Digital (formerly the Health and Social Care Information Centre, HSCIC) NHS Digital is responsible for standardising, collecting and using information and digital technology to improve health and care in England. There are a range of data sets available via the Data Access Requests Service (DARS) department of NHS Digital.

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

Northern Ireland Statistics and Research Agency The Northern Ireland Statistics and Research Agency has responsibility for standardising, collecting and publishing data and information from across the health and social care system in Northern Ireland.

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

Participant Identification Centres (PICs) identify patients for possible participation in trials. They can advertise the opportunities to participate in a specific trial (e.g. by posters in waiting areas) and/or provide information to patients directly about a study that is taking place elsewhere.

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

Patient and Public Involvement (PPI) The process whereby research is carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them; for example, members of the public, such as patients, service users and carers, may be a co-applicant on a grant submission, comment on or develop research materials or become a member of a Trial Steering Committee.

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

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

External pilot A stand alone study planned and undertaken independently of a definitive trial. The data from an external pilot might be analysed but set aside.

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

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

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

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

Reference Safety Information (RSI) Information used for assessing expectedness of an adverse reaction. It is contained in either the Investigator's Brochure or the Summary of Product Characteristics.

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 Costs Research costs are the costs of the research and development itself that end when the research ends. They relate to activities that are being undertaken to answer the research question.

Research Ethics Committee (REC) The body authorised to review documents for research taking place in the NHS, or social services. RECs exist to safeguard the rights, safety, dignity and well-being of research participants. Some RECs specialise in clinical trials, or topics such as research in children.

Research Ethics Service (RES) RES is one of the Health Research Authority's core functions, committed to enabling and supporting ethical research in the NHS. It protects the rights, safety, dignity and wellbeing of research participants.

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

Secure Anonymised Information Linkage (SAIL) SAIL is administered by the Administrative Data Liaison Services (ADLS) in Wales and has responsibility for standardising, collecting and publishing data and information from across the health and social care system in Wales.

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

Service Support Costs (SSC) These are additional patient care costs associated with the research, which would end once the R&D study in question had stopped, even if the patient care involved continued to be provided.

Site Approved location where trial-related activities and assessments are conducted.

Site Initiation Visit (SIV) The visit when site personnel are trained in trial processes. The PI and as many members of the research team as possible should attend, including representation from relevant supporting departments (e.g. pharmacy).

Site-Specific Assessment An assessment performed to establish the suitability of a Principal Investigator and a site for the conduct of research; site-specific assessments will be performed by the participating CRN for each research site (NHS organisation), using 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.

Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) Recommendations for the minimum set of scientific, ethical and administrative elements that should be addressed in a clinical trial protocol.

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

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

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

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

SWAT Study Within A Trial. An embedded methodological research study within an ongoing trial or other prospective study.

Treatment costs Treatment costs are the patient care costs, which would continue to be incurred if the patient care service in question continued to be provided after the research study had stopped.

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

TSC The Trial Steering Committee provides the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and Sponsors.

UK Clinical Research Collaboration (UKCRC) This collaborations' goal is to establish the UK as a world leader in clinical research. The UKCRC provides a forum that enables all Partners to work together to transform the clinical research environment in the UK.

UK Clinical Research Network (UKCRN) Clinical research networks have been established in each of the four UK nations funded by the UK Health Departments. Together these national networks form the UK Clinical Research Network (UKCRN), strategic oversight for which is provided by the UKCRC. The Clinical Research Network is made up of registered CTUs that have been awarded UKCRC Registration by providing evidence to an international panel of experts of their capability to centrally coordinate multisite 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.

UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research in the UK.

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

Introduction

Background

The first edition of the TMN Guide to Efficient Trial Management was produced in March 2000. The fifth edition was produced in 2016, it is from this version that the current group of volunteers working within trials research from all over the UK have come together to produce this new edition.

Purpose

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

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

Application

This Guide contains useful information, guidance and references, 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. The first edition 2018 of the Cancer Supplement to the Guide is now available, see www.tmn.ac.uk/page/guide.

Scope

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

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

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

Use of the Guide

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

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

Limitations of the Guide

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

Section 1 Understanding randomised trials

1.1 Why do a randomised trial?

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

The group that does not receive the intervention being evaluated is called the control group. This group may receive the standard intervention (current best practice/treatment as usual) or, if there is no standard intervention available, no intervention or a placebo (no active treatment) intervention. Trials can involve more than two arms, i.e. there is more than one intervention or procedure being compared with the control group.

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 bias in the estimation of the effect of the intervention. The two primary ways of minimising bias are randomisation and blinding. Chance effects are minimised by including large enough numbers of participants.

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

1.2 Randomisation and methods

Randomisation

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

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

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.

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

Cluster randomisation – the unit of randomisation is not the individual participant being studied but groups of participants. Examples of a cluster could be 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 rather than the individual.

1.3 Blinding (also known as masking or concealing)

Blinding refers to concealing the randomised allocation. This can include blinding investigators, participants and those collecting and analysing the data to knowledge of group assignment. Best practice is that the trial team, especially the trial statistician, should (where possible) remain blind to avoid bias, even in open label trials.

It is very difficult to blind the investigator in some trial designs (e.g. the surgeon in a surgical trial).

1.4 Placebos

Placebos are dummy interventions often used in drug trials. Dummy treatments may also be used in non-drug studies, for example, device and surgery 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 to maintain blinding.

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/intervention 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/intervention 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/intervention and this may reduce compliance. Involving the public (e.g. patients, service users and/or carers) in the trial design can help in anticipating the acceptability of the proposed methods.

1.5 Sample size

The planned sample size or number of participants required is calculated to ensure a high chance of detecting a clinically important difference at a specified level of statistical significance if one truly exists. In order to calculate the sample size, the number of primary events (or event rate), or summary measure of the outcome (e.g. mean), in the control group, as well as its variability, must be known or estimated reasonably accurately so that a realistic estimate of the size of effect of the intervention (e.g. difference in event rates or difference in means) can be made. The minimal clinically important difference should be considered when calculating the sample size. Different trial designs will lead to different calculations and can have implications for the overall sample size. Cluster randomised trials, for example, can lead to a reduction in power compared with individual randomised trials. Adaptive trial designs are increasingly common. This can have an impact on sample size due to potentially inflating the total needed to be randomised (to take into account multiple looks at the data).

When calculating a sample size, consideration should be given to the number of participants whom you expect to receive primary outcome data for and adjustments made to allow for the non-collection of primary outcome data (e.g. participant is lost to follow-up). The sample size must be pre-specified but may be reviewed during the course of a trial, especially if event rates are not well known. The sample size provides the overall recruitment target for the trial and should be outlined in the trial protocol.

1.6 Power

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

1.7 Confidence intervals

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

1.8 Confounding

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

1.9 Outcomes

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

The primary outcome is the most important outcome as it addresses the research question. The sample size is determined with respect to the primary outcome. As a consequence, the primary outcome needs to be one that can be readily assessed and that leads to a feasible sample size. In some circumstances, there may be more than one primary outcome; this will have been considered in trial development and with significant input from the trial statistician. Secondary outcomes chosen should be sufficient to address all relevant aspects of the intervention, but care should be taken to avoid data overload, which is burdensome for both participants and investigators. Some primary outcomes include several elements, known as a composite outcome. This is quite common in some clinical areas e.g. perinatal trials.

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

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

1.10 Types of trials

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

Phase I: first test in humans

Phase I trials are the first stage of testing in humans. Normally, a small group of 20–100 healthy volunteers (HV) will be recruited. These trials are often conducted in a trial clinic, where the participant can be observed by full-time staff.

Phase I trials:

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

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

Phase II

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

Such trials are normally conducted in a group of patients with very specific inclusion/exclusion criteria when it comes to the disease being monitored. They can also include HVs if still assessing safety.

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

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

Phase II trials:

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

Phase III

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

Phase III trials:

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

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

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

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

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

Phase V: comparative effectiveness and community-based research

Phase V is a term used increasingly in the translational research literature to refer to comparative effectiveness research and community-based research. It is used to signify the integration of new treatments/interventions 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 facility level, e.g. a GP practice, school, hospital etc., 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.

Adaptive designs

Trials in which unblinded data are monitored and used to determine the future course of the trial based on prospectively defined decision rules. These can improve oncology trials by providing information leading to better decisions regarding dose and regimen, sample size, target indications and subpopulations in later phases.

Feasibility study

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

Pilot study

A version of the main trial run in miniature to test whether the components of the main trial can all work together. A pilot study reflects the main trial in many components, including an assessment of the primary outcome.

Section 2 National infrastructure

2.1 UK Clinical Research Collaboration (UKCRC)

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

Established in 2004, the UKCRC brings together the major stakeholders that influence clinical trials research in the UK including the main funding bodies, government, charities, academia, the NHS, regulatory bodies, patient groups, industry and consumers in a UK wide environment that facilitates and promotes high quality research for the benefit of patients.

The Collaboration promotes a strategic approach to identifying opportunities and obstacles to clinical research and works collaboratively to resolve issues. Key areas of work relating to trial management are highlighted below. More information on all areas of activity can be found on the UKCRC website at www.ukcrc.org.

2.2 UKCRC Registered Clinical Trials Unit Network

The UKCRC identified Clinical Trials Units (CTUs) as an important element of the UK-wide clinical trials infrastructure. CTUs are specialist units that have been set up with a specific remit to design, conduct, analyse and publish trials and other well-designed studies. Most CTUs will have expertise in the coordination of trials involving investigational medicinal products (IMPs), which must be conducted in compliance with the UK/EU legislation² relating to the conduct of clinical trials.

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

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

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

2.3 UK Clinical Research Network (UKCRN)

Clinical research networks (CRNs) exist across the UK to provide the infrastructure to support high quality clinical studies across all areas of disease and clinical need. Clinical research networks have been established in each of the four UK nations funded by the UK Health Departments and, although the exact structure of the Network varies between countries, all provide the following elements for eligible studies:

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

More information about which studies are eligible for Network support can be found at www.nihr.ac.uk/funding-and-support/study-support-service/eligibility-for-nihr-support/.

When planning a new study it is helpful to liaise with the local Network contact to discuss the study and resource implications to ensure network support in the longer term. If the CI is based in a different geographical

location to the trial manager, it is normal to have these discussions with the Network where the CI is based. During the course of the study the Network can be a valuable contact point to resolve site specific issues such as low recruitment or data return rates. Further information regarding the CRNs and related infrastructure can be found on the relevant country-specific host websites.

In England the Clinical Research Network is made up of 15 Local Clinical Research Networks. The CRN delivers research across 30 clinical specialties at a national and local level. The NIHR Clinical Research Network Coordinating Centre manages the CRN on behalf of the Department of Health. The CRN provides the infrastructure that allows high-quality clinical research to be undertaken throughout the NHS. They work with patients and the public to make sure their needs are placed at the heart of all research and provide opportunities for patients to gain earlier access to new and better treatments through research participation. Contacts for each can be found at www.nihr.ac.uk/about-us/how-we-are-managed/managing-centres/crn/.

In Scotland there are seven topic-specific clinical research networks, established by the Chief Scientist Office (CSO). These Networks provide the infrastructure to support a range of high quality studies across many areas of disease and clinical need in Scotland. The CSO has encouraged NHS Scotland and the clinical academic research community to plan the expansion of its clinical research activity in a collaborative way and to work with partner networks across the UK. Contacts can be found at www.cso.scot.nhs.uk/nrs/.

In Northern Ireland the Health and Social Care (HSC) R&D Office has established the Northern Ireland Clinical Research Network (NICRN) to provide research infrastructure as part of the UKCRN. This managed, comprehensive network has a Coordinating Centre based at the Belfast Royal Hospitals site and comprises nine NICRN areas of interest. These are networks of clinicians and other professionals with a critical mass of research interest in specific disease areas and with access to a sufficiently large patient population to enable recruitment. Contacts can be found at: www.nicrn.hscni.net/.

In Wales the clinical research infrastructure is provided by the Welsh Government through Health and Care Research Wales. Health and Care Research Wales provides an infrastructure to support and increase capacity in R&D, runs a range of responsive funding schemes and manages resources to promote, support and deliver research in health and social care. Further information can be found at: <https://www.healthandcareresearch.gov.wales/>.

2.4 Health Research Authority (HRA)

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

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

The HRA website provides up to date information on all areas of work, see www.hra.nhs.uk/.

Section 3 Ethical and regulatory framework

3.1 Legislation and guidance

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

TABLE 1 Key legislation, guidance and approvals required

	Key legislation and guidance	Required approvals*
All trials	<ul style="list-style-type: none"> Guidelines for Good Clinical Practice (GCP) www.gov.uk/guidance/good-clinical-practice-for-clinical-trials 	<ul style="list-style-type: none"> Health Research Authority (www.hra.nhs.uk)
	<ul style="list-style-type: none"> UK Policy Framework for Health and Social Care Research 2017³ (www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/) 	<ul style="list-style-type: none"> NHS Permissions (NHS/HSC R&D offices)
	<ul style="list-style-type: none"> Data Protection Act 2018⁴ (www.legislation.gov.uk/ukpga/2018/12) 	<ul style="list-style-type: none"> Research Ethics Service (RES) (www.hra.nhs.uk)
	<ul style="list-style-type: none"> Freedom of Information Act 2000⁵ 	
In addition, for clinical trials of medicinal products	<ul style="list-style-type: none"> Medicines for Human Use (Clinical Trials) Regulations 2004⁶ and its amendments 2007, 2008⁷ 2006a⁸ 2006b⁸ 2008⁹ and 2009¹⁰ (www.legislation.gov.uk/uksi/2004/1031/contents/made www.legislation.gov.uk/uksi/2006/2984/pdfs/uksi_20062984_en.pdf) 	<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 2002¹¹ The Medical Devices (Amendment) Regulations 2003¹² 	<ul style="list-style-type: none"> Trials of non-CE-marked medical devices and CE-marked medical devices used for new indications MHRA approval
In addition for clinical trials of advanced therapy investigational medicinal products *	<ul style="list-style-type: none"> Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010 (SI 2010 No.1882) The Human Tissue (Quality and Safety for Human Application) Regulations 2007 (SI 2007 No.1523) Genetically Modified Organism (Contained Use) Regulation 2014 (SI 2014 No.1663) Genetically Modified Organism (Deliberate Release) Regulation 2002 (SI 2002 2443) Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2009_11_03_guideline.pdf) 	<p>Local Genetic Modification Safety Committee (GMSC) review and opinion of risk assessment for GMOs</p> <p>Notification to Health and Safety Executive (HSE) for first time use of GMO at premises and/or class 2/3/4 product activities</p>
Other	<p>*Depending on the specifics of the trial, approvals may be required from the following review bodies:</p> <p>Mental Capacity Act 14 2005¹³ (non-CTIMPs only)</p> <p>Human Tissue Act 13 2004¹⁴ (only if collecting human tissues)</p>	
	Administration of Radioactive Substances Advisory Committee	
	Gene Therapy Advisory Committee	
	Ministry of Defense Research Ethics Committee	

Other (contd)	Health Research Authority (included components of work undertaken formerly by the National Information Governance Board)	
	National Offender Management Service	
	Social Care Research Ethics Committee	
	Expert Advisory Group/the Commission on Human Medicines review for certain first-in-human trials	
	Her Majesty's Prison and Probation Service (HMPPS) (www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/prison-research/)	
	Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG) of the Commission on Human Medicines review for certain first-in-human trials	
	Confidentiality Advisory Group (CAG)	

UK Policy Framework for Health and Social Care Research

The UK Policy Framework for Health and Social Care Research sets out principles of good practice to ensure that all research undertaken within NHS health and social care organisations conform to a common set of standards. The principles set out in the policy protect and promote the interests of patients, service users and the public by describing ethical conduct and proportionate management of health and social care research. It is for organisations and individuals that have responsibility for the conduct of research in the NHS health and social care organisations and replaces the separate research governance frameworks in each UK country with a single policy for the whole of the UK. More information is available at www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/.

World Medical Association 'Declaration of Helsinki'

A statement of ethical principles for medical research involving human subjects, including identifiable human material and data. There are a number of versions, with the most recent available on the WMA website see www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

Good Clinical Practice – all trials

Good Clinical Practice principles are based on providing assurance that the data and reported results of clinical investigations are credible and accurate and that the rights, safety and confidentiality of participants in clinical research are respected and protected. There are a number of different standards which are essentially based on the same set of principles. For CTIMPs the principles set out in the Medicines for Human Use (Clinical Trials) Regulations 2004⁶ and the EU Directive on Good Clinical Practice² are a legal obligation in the UK/Europe; for non CTIMPs equivalent standards set out by the Medical Research Council are acknowledged as good practice. ICH-GCP¹⁵ is an international set of standards which applies to clinical trials for registration purposes.

General Data Protection Regulation (GDPR) and Data Protection Act 2018

The General Data Protection Regulation and the Data Protection Act 2018 is new legislation that places obligations on those who process information (data controllers) while giving rights to those who are the subject of the data (data subjects), see www.legislation.gov.uk/ukpga/2018/12.

In order to hold and/or process data, a clear legal basis is required. Joint data controllers are permitted e.g. where a clinical trials unit is involved. It applies where any 'personal data' (as defined by the Act) are being collected, held or processed. The Act also defines a special category of personal data as 'sensitive' and the lawful use of these data are further restricted under the Act. Obtaining consent to take part in research and for disclosure of confidential information is important, GDPR does not change this, however, GDPR's consent requirements do not often apply to research. 'Task in the public interest' is the most appropriate lawful basis when processing data for research in the NHS and universities. For research controlled by charitable organisations and commercial companies it is 'legitimate interest', not consent. GDPR says any personal data can be used for research regardless of initial reason for collection, subject

to safeguards, transparency and fairness. Data minimisation means that data must be adequate to properly fulfil the purpose, but limited to what is necessary for that purpose. Where possible data should be anonymised. When sharing confidential information with other researchers the participant's permission should be gained, see www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/ and <https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/gdpr-resources/>.

Processing activities should reflect what participants have been told, for example if audio data is going to be transcribed by a third party consent is required. Where there are new uses of data, participants need to be informed and given the opportunity to object. The HRA have produced some transparency wording that explains what research is and what can be expected. An organisational transparency notice can be used in conjunction with project specific transparency information to inform participants how their data will be processed.

Researchers should consult their Data Protection Officer (DPO) if a request for data to be deleted is received. Research is largely exempt from the right to erasure, so all data about a participant doesn't necessarily have to be deleted. A researcher may choose to delete some or all of a participant's data, but they need to work out how deletion can be achieved and what impact it will have on the integrity of the research, compliance with other regulations and the risk of re-contacting the participant in the future.

The Freedom of Information Act 2000 (FOIA)

The Freedom of Information Act 2000⁵ gives individuals a general right of access to information held by or on behalf of public authorities. A public authority must reply within 20 working days to any written FOIA request received from an individual to inform them whether or not the public authority holds information and, subject to exemptions, supply them with that information, see www.legislation.gov.uk/ukpga/2000/36/contents.

More information and guidance is available from The Information Commissioner's Office, see www.ico.gov.uk.

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

The Mental Capacity Act 2005¹³ is relevant to research involving adults over the age of 16 years in England and Wales. In Scotland, the Adults with Incapacity (Scotland) Act 2000 applies¹⁶. There is no specific legislation in Northern Ireland; however, there is the common law of consent. The Mental Capacity Act does not apply to CTIMPs. The Medicines for Human Use (Clinical Trials) Regulations 2004⁶ make legal provision for participation in CTIMPs by adults lacking the capacity to consent and the endurance of consent after the loss of capacity, see www.england.nhs.uk/ourwork/safeguarding/our-work/mca/.

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

A helpful toolkit and other resources are available, see The Health Research Authority www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/mental-capacity-act/.

The Human Tissue Act 2004

The Human Tissue Act 2004¹⁴ came into force on 1 September 2006 and it is a statutory framework for dealing with issues relating to whole body donation and the removal, storage and use of human organs, tissue and anything containing human cells, including for research purposes. Consent from the donor or nominated representative is the fundamental principle of the Human Tissue Act.

There is separate legislation in Scotland: the Human Tissue (Scotland) Act 2006¹⁷. While provisions of the Human Tissue (Scotland) Act 2006 are based on authorisation rather than consent, these are essentially both expressions of the same principle.

More information and advice is available, see

- The HTA legislation, policies and codes of practice www.hta.gov.uk.
- Human tissue legislation summaries <https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/human-tissue/>.

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 human' 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).⁶

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

More information and advice is available, see

- MHRA website www.mhra.gov.uk.
- Eudralex website http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm.
- Medical Research Council/ MHRA/Department of Health joint project on risk-proportionate approaches to the management and monitoring of clinical trials¹⁹.
- The Clinical Trials Toolkit www.ct-toolkit.ac.uk.

EudraCT

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

Clinical Trials of Investigational Medicinal Products (CTIMPs) New Regulation

The EU legislation for clinical trials is changing. The EU Clinical Trials Regulation (No 536/2014) on clinical trials of medicinal products for human use and the repealing of Directive 2001/20/EC is likely to become applicable in 2019. The date of applicability relates to the development and confirmation of full functionality of a new EU Portal and EU database. The date of applicability will be published in the Official Journal of the European Union. Transition periods will apply; however, organisations will be required to make changes to their processes and Trial Managers should make themselves aware of the key dates as they are made public.

Clinical Trials of Advanced Therapy Investigational Medicinal Products (ATIMP)

Advanced Therapy Medicinal Products can be classified as Gene Therapy, Cell Therapy or Tissue Engineered products. All regulatory requirements related to CTIMPs are applicable to clinical trials of ATIMPs, but there are additional requirements and considerations to be taken into account depending on the type of product under investigation. All clinical trials involving ATIMPs must comply with Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products.

All trials of Gene Therapy Medicinal Products must legally be submitted to the Gene Therapy Advisory Committee (GTAC), which is the UK national REC for gene therapy clinical research. GTAC will also review trials of Cell Therapy medicinal products. If an ATIMP incorporates a medical device it could be classified as a combined ATIMP, in which case the medical device directives may also be applicable, depending on the nature of the device component. Obtaining advice from the MHRA on requirements for CTA submission of a combined ATMP would be advised.

The European Commission (EC) guidance on GCP for ATMPs sets out in detail the additional GCP requirements and considerations for ATIMP trials, including safety, traceability, essential documents and long-term follow-up requirements, see https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2009_11_03_guideline.pdf.

The Human Tissue (Quality and Safety) Regulations 2007 apply to the donation, procurement, import and testing of tissues and/or cells that will be used as starting materials for the manufacture of ATIMPs. An appropriate HTA Human Application license issued by the Human Tissue Authority may be required at applicable trial sites to cover these activities.

More information and advice is available at:

- HTA Website www.hta.gov.uk/policies/regenerative-medicine-and-regulation-advanced-therapies-medicinal-products-atmps and www.hta.gov.uk/regulated-sectors/human-application.

The Genetically Modified Organism (GMO) (Contained Use) Regulations 2014 apply to the use, storage, modification, transport and destruction of IMPs classified as GMOs, which includes some types of Gene Therapy Medical Products. The Health and Safety Executive (HSE) are the overseeing regulatory body that must be notified of the first use of a premises undertaking GMO activities and for each separate project where the product is classified as class 2 or above. In the UK most IMPs classified as a GMO fall under the GMO (Contained Use) Regulations 2014 although it is possible that the activities could be considered deliberate release. GMO (deliberate release) Regulations 2002 are regulated by the Department for Environment, Food and Rural Affairs, if in doubt the HSE can be consulted for an opinion. Trial sites must undertake a Genetic Modification risk assessment which must be reviewed by a local Genetic Modification Safety Committee prior to the commencement of the trial.

Clinical Trials of Medical Devices for Human Use

Clinical trials of medical devices for human use that do not have a CE mark, or a CE marked device being used outside its licensed indication have specific regulations, both nationally and internationally and must comply with The Medical Devices Regulations 2002¹¹ and the Medical Device (amendment) Regulations 2012. 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 14155²⁰, should be adhered to in order to guarantee a high standard of quality. For further information, see

- MHRA www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.
- International Organization for Standardization www.iso.org/.

IRMER Regulations

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

More information and advice is available at:

- HRA ionising radiation resource page: www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/ionising-radiation/.

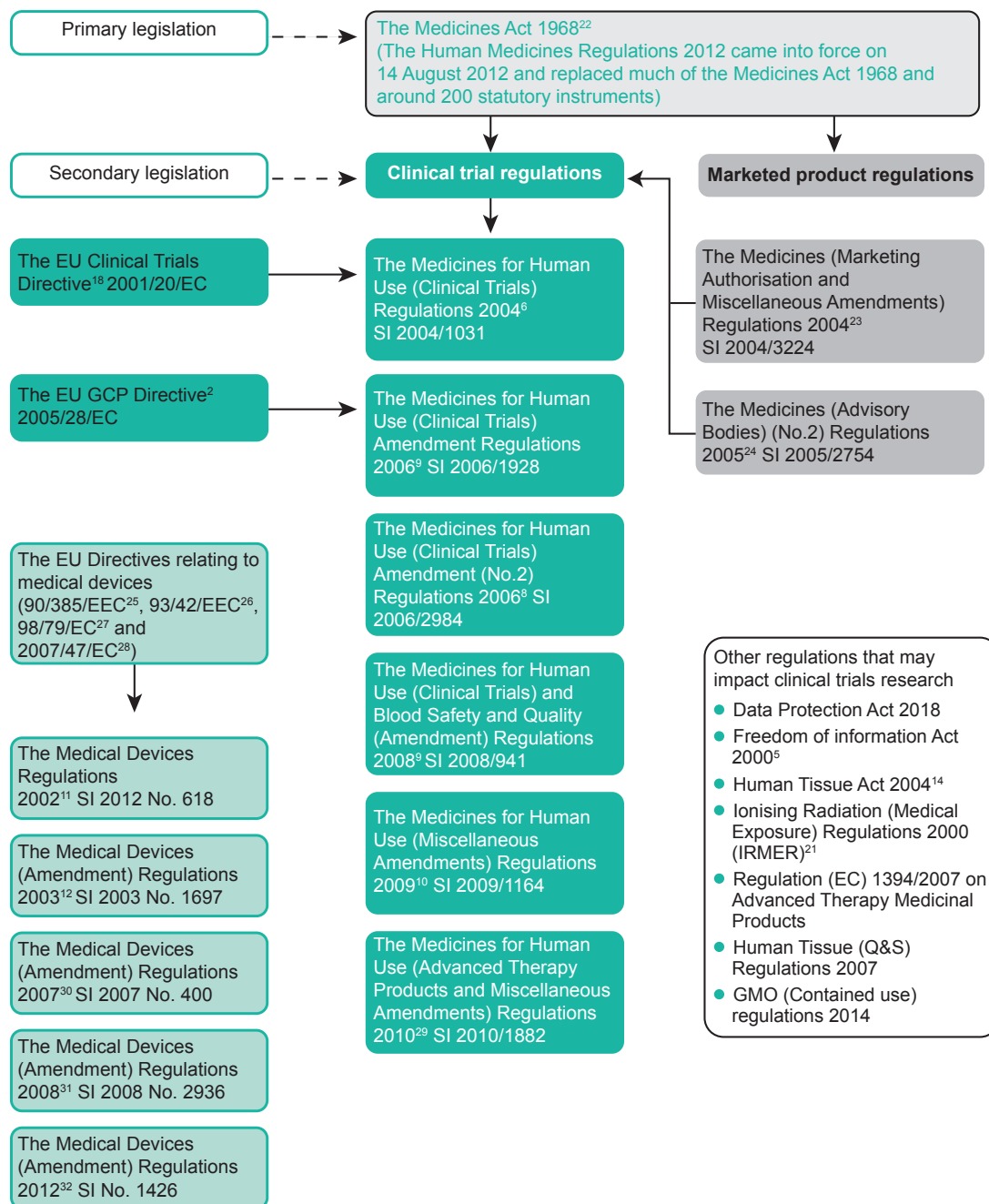


FIGURE 1 Key regulations relevant to CTIMPs and medical devices in the UK

3.2 Systems for approvals and permissions

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

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

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

Chief Investigator checklist (before seeking approvals)

A useful checklist can be obtained from the Clinical Trials Toolkit. The checklist has been provided to ensure all appropriate issues are considered prior to seeking approvals, see www.ct-toolkit.ac.uk/routemap/ci-checklist-before-seeking-approval.

Sponsorship

All clinical research within the scope of the UK Policy Framework for Health and Social Care Research 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.

For CTIMPs the Sponsor has specific legal obligations which are detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004;⁶ see the Clinical Trials Toolkit Sponsorship Station www.ct-toolkit.ac.uk/routemap/sponsorship.

Clinical trial registration

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

It is government policy in the UK to encourage voluntary registration of trials and other well designed studies on publicly accessible registers such as ISRCTN, <https://clinicaltrials.gov/>.

Clinical trial registration is not mandatory for all trials although:

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

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

Ethical approval

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

All research taking place in the NHS in England requires approval for the research to commence via HRA Approval. This comprises a review by a Research Ethics Committee and an assessment of regulatory

compliance, which includes where relevant a pharmacy and radiology assessment. NHS ethics approval is obtained using the centralised system called IRAS (Integrated Research Application System).

Integrated Research Application System (IRAS)

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

For further information, see IRAS guidance and a training e-module is available once you have logged into the IRAS website www.myresearchproject.org.uk/Signin.aspx then www.myresearchproject.org.uk/Help/HelpPage.aspx.

Gaining NHS permission for clinical research

All trials that involve NHS staff, patients, patients' samples, records or facilities, require approval by the R&D Department at the relevant NHS site. 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.

The R&D Department will review the proposal for the trial to ensure they have both the capacity and capability of undertaking the trial. To do this they will consult with a range of staff and departments to ensure all facilities are on-board and the trial has been costed appropriately.

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

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

1. England and Wales: In April 2018 HRA Approval became HRA and Health and Care Research Wales (HCRW) Approval and now applies to all project-based research taking place in the NHS in England and Wales. For further details of English led projects, see www.hra.nhs.uk/planning-and-improving-research/best-practice/nhs-site-set-up-in-england/ and for Welsh led www.healthandcareresearch.gov.wales/.
On the HRA site you will find links to the Statement of Activities and Schedule of Events templates that should be used to provide information on participating NHS organisations in England and Wales. A Statement of Activities for each site type should be completed and accompanied by a completed Schedule of Events as part of your submission. The two documents allow the Sponsor to make clear what activities will be undertaken locally and the cost type for each activity.
2. Scotland: NHS Research Scotland Permissions Coordinating Centre, see www.nhsresearchscotland.org.uk/services/uk-wide-working/iras.
3. Northern Ireland: Health and Social Care Application Gateway, see www.hscni.net.

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

3.3 Data registries and routine datasets

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 the trial intends to access registry data, approval will be needed from these agencies in addition to ethics committee approval and a CTA (if appropriate). Specific details about the services to be used must be included in the patient information leaflet (PIL) and consent form, including a list of personal details which will be used to match data in the registry. Some 'registries' will require specific wording to be included in the patient information leaflet and consent form so checking the policy of the registry at the time the PIL and consent are being prepared is advised. Note: the NHS number and, in Scotland, the Community Health Index (CHI) number, a unique 10-digit patient identifier, should be collected to enable tracking.

Routinely collected data

Routinely collected data is defined as data collected for routine purposes other than research. Increased ability to store, process and access large amounts of Routinely collected data has led to increasing usage for research³³.

Data linkage services

There are several services that provide access to routinely collected data and are different for each geographical area of the UK.

NHS Digital - England

NHS Digital (formerly the Health and Social Care Information Centre, HSCIC) has responsibility for standardising, collecting and publishing data and information from across the health and social care system in England. There are a range of data sets available via the Data Access Requests Service (DARS) department of NHS Digital. For up to date information on what data sets are available and how to access them, see <https://digital.nhs.uk/>.

Information Services Division (ISD) – Scotland

The ISD is part of NHS National Services Scotland and has responsibility for standardising, collecting and publishing data and information from across the health and social care system in Scotland. For up to date information on what data sets are available and how to access them, see www.isdscotland.org.

Secure Anonymised Information Linkage (SAIL) – Wales

SAIL is administered by the Administrative Data Liaison Services (ADLS) and has responsibility for standardising, collecting and publishing data and information from across the health and social care system in Wales. For up to date information on what data sets are available and how to access them, see <https://saildatabank.com/>.

Northern Ireland Statistics and Research Agency – Northern Ireland

The Northern Ireland Statistics and Research Agency has responsibility for standardising, collecting and publishing data and information from across the health and social care system in Northern Ireland. For up to date information on what data sets are available and how to access them, see www.ninis2.nisra.gov.uk/.

Section 4 Trial planning and development

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

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

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

The five basic process stages of any project are:

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

Good project management skills are an essential part of a Trial Manager's role. It is important to have clear project plans and realistic timelines; evaluate risk and plan contingency; establish clear processes; coordinate resources including staff; monitor progress and quality assurance recognising where processes could be improved and implementing the necessary changes.

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

- **Scope/quality:** this includes ensuring that the requisite number of participants are recruited and that recorded data is of the highest quality; this needs careful initial planning and subsequent management.
- **Budget:** risks to budget should be minimised during the planning stage. A review of expenditure should be performed regularly throughout the trial to ensure potential overspend is identified early enough to mitigate. Funding extensions are both time consuming and difficult to justify and so should be avoided wherever possible.
- **Timelines:** it is essential that realistic timelines are planned initially and reviewed regularly during the trial. It may sometimes be necessary to extend trial timelines, for example as a result of delays to approvals or slow recruitment of participants, however obtaining additional funding for this is not guaranteed. Additional time can be requested but must be fully justified and requested early. For a commercial trial, timelines may be a higher priority than budget. Many funders now request a feasibility study or a pilot phase before committing to funding the whole study. This can be important to ensure the required population is available and to identify any obstacles.

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

- Identifying and mitigating risks (see Section 4.3). All risks to the trial should be rated in terms of likelihood of occurrence and impact:
 - ➔ Major risks (high likelihood and high impact) should be reduced or avoided by re-planning.
 - ➔ Medium risks (high likelihood or high impact) should have mitigating strategies put in place.
 - ➔ Minor risks (low likelihood and low impact) should be documented.
- Maintaining good communication with all relevant parties.
- Determining the work required and developing a schedule with milestones, i.e. identifying what needs to be achieved. A simplified Gantt chart may be useful to show projected timelines and where activities are dependent on other milestones being met and where they can be performed in parallel. This is particularly relevant at the set-up stage, e.g. regulatory submission requires having appointed the packager for the IMP.

- Determining the resources required during the stages of the trial and the associated budget schedule.
- Monitoring quality, timelines, budget and resources in comparison with the trial and budget schedules, determining the cause and impact of any variance and taking corrective action where required. Changes in scope, for example, adding extra sites or increasing recruitment targets also need to be managed carefully and the impact on the trial needs to be analysed.
- Managing the trial efficiently by disseminating appropriate information to all those involved in the trial, ensuring that everyone is aware of their role, the timelines 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) 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. Patient and public involvement (PPI) is an expectation of NIHR funding applications and there is evidence that it can improve participation recruitment and retention in trials. The RDS can help advise on building patient and public involvement into the design and carrying out of trials, see www.rds.nihr.ac.uk.

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

Preparing the grant application

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

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

It is useful to do a full costing at the outline stage as the budget in the full application should not differ significantly.

Most funders have online application forms but they usually also require a formal 'sign-off' by the CI, the head of department or institution, the administrative authority (typically a university or NHS trust where staff, facilities or patients are based) as well as financial approval by the host institution. The team should notify the approvers in advance to discuss any potential issues and be clear on institutional timelines.

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, UK Research and Innovation (UKRI), members of the Association of Medical Research Charities (AMRC) and most other funders will comprise three cost types:

- Research Costs: costs attributed to the funder body for 'conducting' the research.

- Service Support Costs: met from R&D budgets of the health departments of the UK; in England this is often via the CRN. Such costs include the participant care costs, which would end once research completes, even if the treatment/intervention continues, e.g. appointments to obtain consent or in-patient stays for research purposes.
- Treatment Costs: covered by NHS commissioning arrangements. These include care costs that would be ongoing if the treatment/intervention continued in 'real care', for example: drug/intervention costs, (including administration and infusion time) and therapist time. The difference between standard treatment and the experimental treatment cost is referred to as the 'Excess Treatment Cost' (ETC). In calculating ETCs, the intervention is assumed to be successful and adopted into routine care. If ETCs are substantial, subvention funding may be available though, unless ETCs are extremely high per Trust, they are expected to be met by the Trust.

In England, industry-funded but academically led/sponsored trials are not eligible to receive support costs or treatment costs unless adopted onto the NIHR portfolio. Industry-sponsored studies operate at full cost recovery. More detailed information can be found in the funders' guidelines.

Further information about these different costs is given in the Department of Health's document: Attributing the costs of health and social care research and development (AcoRD), see https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/351182/AcoRD_Guidance_for_publication_May_2012.pdf.

Costing a research grant

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

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

Trial/research budget checklist

- Salaries for trial staff including (but not limited to) statisticians, health economists, qualitative researchers. In a CTU it will usually be possible to have varying % of full-time staff at different stages of the trial: e.g.30% of a statistician during the set-up and running of a trial and 100% during the analysis.
- IMP/intervention/device costs including: drug/placebo manufacture, labelling, blinding, device or intervention purchase, testing, shipping and destruction and unblinding arrangements.
- Equipment purchase, testing and delivery e.g. centrifuges, freezers, monitors.
- MHRA fees.
- Laboratory or other test fees; couriers for moving specimens, long-term storage of samples.
- Accessing routine data, e.g. via the Data Access Request Service at NHS Digital, or equivalent outside of England. There are a number of datasets that are available via this service.
- Randomisation system development or purchase.
- Database design/data collection system, development or purchase, licenses, hosting fees.
- Computing: hardware, software, computer consumables.
- Web design costs.
- Printing and postage costs: protocols, consent forms, data forms, questionnaires, posters and

newsletters, Freepost licence (for participants to return questionnaires). Note: allow for postage cost increases over time and multiple mailings for non-responders. Utilise web distribution for newsletters and/or questionnaires to reduce costs where possible.

- Consumables: stationery, office furniture, filing cabinets, photocopying (these may not be allowed by certain funders if they are already covering overheads/indirect costs).
- License fees for questionnaires.
- Participant expenses and incentives: small gifts, pens or gift vouchers and participant travel expenses (subject to funder and ethical approval).
- PPI involvement: travel expenses, out-of-pocket expenses, payment for involvement and meeting attendance, any support and training.
- Telephone/fax/email: to maintain regular contact with sites and participants, include text messages if appropriate.
- Advertising costs if used to aid recruitment.
- Site costs: telephones, internet, photocopying, fax, data collection, nursing support staff and other site staff, archiving at site.
- Travel for site visits for initiation, training, monitoring and close-out meetings. Also include researcher costs, possibly including accommodation and subsistence.
- Meetings: trial management, oversight committee meetings (e.g. TSC, DMC). Additional costs may include room hire, travel and refreshments. Consider opportunities to reduce the trial carbon footprint and reduce costs, e.g. teleconferencing/online meeting facilities.
- Publication and dissemination: Journal publication fees (e.g. for publishing protocol, main results paper and subsequent publications) and fees for attendance at conferences.
- Archiving and storage: sufficient resources will be needed to allow archiving according to the appropriate regulations (see section 9).
- Consider also if a methodological study within a trial Study Within A Trial (SWAT) can be easily included (see section 6).

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

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

4.2 Public involvement

Involving the public in your trial can help to improve the quality, relevance and acceptability of the trial to potential trial participants. This section has been written with the assistance of INVOLVE which is a national advisory body funded by the NIHR to lead the advancement of public involvement in NHS, public health and social care research in the UK and beyond, see www.involve.nihr.ac.uk.

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

Improving the quality and acceptability of the trial by:

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

Making the research more relevant by:

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

It should be noted that, unlike recruiting participants into trials, involving people in trials in a research advisory, consultative or collaborative capacity does not require specific ethical approval, www.invo.org.uk/posttypefaq/do-i-need-to-apply-for-ethical-approval-to-involve-the-public-in-my-research/.

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.
- Do not 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 PPI representatives. 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 do 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.
- 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. Provide a guidance document which identifies some key principles and features involved in co-producing a research project: www.invo.org.uk/posttypepublication/guidance-on-co-producing-a-research-project/. Over a programme of research, more experienced patients may be able to take on a mentoring role with newer members of the public.
- Trials are complicated so people need to be well supported.
- Think about people's personal development. It is important to consider what the people involved in the research are getting from the experience as well as the impact on the research. Developing people will also benefit future trials that they are involved in.
- Establishing and maintaining good communications is vital for successful involvement and bear in mind the advice about flexibility. Some people prefer phone calls, some like emails. Some will be comfortable with teleconferencing, but for others this may be a difficult and ineffective way for them to contribute.
- Plan to provide feedback to the people you involve to let them know how their contribution has helped

or be able to explain where you haven't been able to take their views on board. People often feel they are consulted, without seeing any change as a result.

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

4.3 Risk assessment

The purpose of risk assessment is to identify potential risks associated with the trial, to assess the likelihood of those risks occurring and to put plans in place to mitigate against those risks. The risks could be to the participant, the organisation(s) involved and to the integrity of the trial. This assessment should inform the development of relevant risk-mitigation plans along with proportionate trial management and monitoring plans.

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

The risk assessment may be led by the Sponsor/Chief Investigator/Trial Manager or protocol author but should include input from the QA person and all 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:¹⁹

- the risks to participant safety in relation to the intervention and clinical procedures.
- the risks to participant rights.
- the risk to reputation (trial team/funder/institution).
- 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 of the risks for the trial. This documentation, which may be included in the protocol or in trial-specific procedures and plans, will not only facilitate the management of the trial but can be used in the course of an audit or regulatory inspection to justify the approaches taken.

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

Active Sponsor and trial team oversight and regular reviews of the risk assessment during the course of the trial are essential in any risk-adapted model. This will ensure that there is escalation/moderation of activity in response to incoming data and feedback on trial progress and conduct. Risk assessment documentation should be updated when reviewed. If no changes are required, evidence that the review has taken place should be filed in the TMF.

4.4 The trial protocol

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

It is important to note that the trial Sponsor may also have protocol guidelines and templates which may need to be followed.

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.
- Ensure that it has a structure that is logical and flows and that items follow through the different sections. This is particularly important when making amendments: cross-check the implications of every change throughout the document.
- A protocol for a CTIMP may be very different in size and scale to a small observational study – it has to be appropriate and proportionate.
- Protocols tend to be lengthy, complex documents. Proofreading by others is key.
- Public involvement in the design of the protocol can help in assessing potential feasibility and acceptability to participants.
- Consistency in terminology, phrases and procedures is crucial; consider creating and using a style guide. A glossary can also be useful.
- Evidence of clinical equipoise is important. Strong opinions about a particular treatment can be unhelpful.
- Every protocol will need amendments but, as the number increases, so does the workload and the goodwill of sites may decrease. As a result it is advisable to ensure that your protocol is fit for purpose from the start.

Writing a trial protocol

- There should be one individual with editorial control and oversight of the writing process. This person can also coordinate sections created by others, for example the statistical outline.
- Appoint a protocol writing group. A protocol needs input from many different people and this process needs careful management.
- Do not reinvent the wheel. If you have a similar research project with a good protocol, use that as a template. Many sponsors have protocol templates which you may be required to use.
- Peer review of the protocol will ensure it is fit for purpose.
- Implement strict version control and an archiving policy.
- Writing a protocol will take longer than you anticipate. Plan carefully and devise a realistic timeline.

Protocol and trial publications policy

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

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

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

4.5 Randomisation options

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

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

External systems include central telephone randomisation, web-based systems, email or fax to the Coordinating Centre and automated electronic systems with voice-mail recognition. An automated electronic system with voice-recognition or a web-based system is the optimal method of randomisation as it is set up by independent operators and captures baseline details as soon as the participant is entered into the trial so they can be tracked for outcome data. The treatment allocation is held electronically and is secure. Web-based systems can be developed to send both unblinded and blinded randomisation emails simultaneously to different parties, maintaining blinding but ensuring parties are aware of the randomisation taking place.

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

Discuss the randomisation method to be used with sites to ensure they are able to undertake this. The trial may use an external system primarily, but will have a back-up internal system process in case the external system fails, particularly in trials with a limited recruitment window.

4.6 Trial oversight

Arrangements for the oversight of trials will vary according to the nature of the trial and should be proportionate to the complexity and associated risks. Different funders may also have particular requirements. Trial managers should always work to the specific requirements of the funder and Sponsor.

Commonly, trials are overseen by three committees: the Trial Management Group (TMG), the Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC). The arrangements for trial oversight should be detailed in the protocol.

Trial Management Group

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

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

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

Trial Steering Committee

The role of the TSC is to provide independent oversight of the trial on behalf of the Sponsor and funder and to ensure that the trial is conducted in accordance with the principles of GCP and relevant regulations. The TSC should focus on the progress of the trial, adherence to the protocol and participant safety. In addition, the TSC should review any relevant emerging information regarding the intervention or clinical procedure that may have an impact on the trial. The terms of reference/charter 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 public/patient representative/s. 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. Funders (e.g. NIHR) often have specific requirements for membership of the TSC and wish to approve specified members.

Data Monitoring Committee

The role of the DMC is to monitor accumulating data from the trial at pre-specified intervals, in particular in relation to safety and efficacy and make recommendations to the TSC regarding any safety issues that should be brought to the attention of investigators or any ethical reasons why the trial should not continue. Usually the DMC is the only group to have access to unblinded data during the course of the trial. In addition, it considers

whether or not any interim analyses are required and would review these data (applicable to blinded trials only). All members should be totally independent of the trial. The DMC usually includes three or four members and 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. Funders (e.g. NIHR) often have specific requirements for membership of the DMC and wish to approve specified members.

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.

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

Meetings are usually held every 6 to 12 months. However, the DMC can meet more frequently if necessary. Meetings should be scheduled prior to the date of the TSC meetings to allow enough time for the Chair of the DMC to report to the Chair of the TSC.

4.7 Regular reporting

It is very important to consider what reports will be required, who you have to report to and when. This will ensure that reporting milestones are met. Funding bodies have rules for what needs to be reported, including some outputs or where they need to be informed of activities, for example, NIHR HTA consider participants' materials to be outputs, see www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/manage-my-study/outputs-guidance-notes-2.pdf. For CTIMPs that have received IMP in kind from a Pharmaceutical company, they will often request regular progress reports.

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

Which bodies need a report?

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

What types of reports are required?

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

Who will produce reports?

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

How often are reports required and in what format?

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

Check format required for submission, e.g. electronic or paper.

What data are required to be included in the report?

Information such as, recruitment data, safety data, blinded or unblinded data.

Financial reporting:

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

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

The CTUs responsible for a portfolio of trials:

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

Section 5 Trial set-up

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

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

5.1 Trial Coordinating Centre

What is a trial Coordinating Centre?

The trial Coordinating Centre is at the heart of the trial, whether it is a single-site or multisite 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.
- split over different locations and can be a combination of the above, for example a CTU can support an academic department in one or more aspects of running a trial (data management, statistics etc).

The Coordinating Centre will need:

- contracts or agreements with: the funder, the Sponsor and the host institution (which may also be the Sponsor) which will determine delegated tasks, space, staff and equipment and any other institution/ subcontractor that is undertaking an aspect of the trial.
- systems for data management, administration, finance and personnel management.

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

A typical Coordinating Centre trial team consists of the following:

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

The trial team will usually have been determined whilst preparing the grant application and the percentages of staff time required should have been costed at this stage. For example, the trial may require two data assistants but only 50% (or 0.5 FTE) of an IT programmer. Begin to incorporate the functions, responsibilities, competencies required and likely workload hot spots as part of the project management plan.

5.2 The trial team

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

Chief Investigator

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

Trial Manager

Excellent trial management is the key to successful trial delivery. The Trial Manager coordinates and is responsible for the day-to-day activities of a trial and therefore holds a pivotal position. Successful trial managers need to be multitasking with good leadership skills, hard-working, well organised with an ability to multi-task, capable of decision-making and excellent communicators. Never underestimate the importance of common sense and attention to detail. Further details of the competencies required to be a trial manager can be found at www.tmn.ac.uk/page/TKCFramework?&hhsearchterms.

Administrative support

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

IT Programmer

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

Data Manager

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

Data Assistant

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

Statistician

The role of the Statistician is to ensure that the sample size estimation is accurate, that the interim and final analyses mirror the outcomes in the protocol and that the analyses are conducted according to a Statistical Analysis Plan. Therefore, a trial will rarely need full-time statistical support as their input is concentrated around the planning phase, monitoring data quality, interim and final analyses. This aspect of a trial could be provided by someone outside the Coordinating Centre, however, the trial statistician is a key member of the trial management group and would be expected to attend and provide data for TMG meetings. It is essential that the Statistician is committed and involved from the start of the trial (ideally at the grant writing/protocol writing stage) to ensure that the data required will be collected.

Patient or Public member(s)

Depending upon the nature of the trial, patients or member(s) of the public might be co-applicant(s) with a defined role within the trial. Public co-applicants will have specific role(s) formally agreed in advance of the trial work beginning and the nature of the role will depend upon the needs of the trial and the skills, knowledge and expertise of the co-applicant. For example, public co-applicants may share first-hand experience of the priorities of patient or public communities affected by the trial participants. They may also act as a link to wider patient/public audiences to include broader, more diverse perspectives which inform recruitment or retention approaches. Public co-applicants may also help with trial procedures and reporting, while ensuring that patient-facing information is optimal from a patient or public perspective.

It is important that someone on the team takes responsibility for the planned public involvement before, during and after the trial. Certain skills are required for this role and sufficient time needs to be allocated so that support is available to the public or patient member/s of the team to maximise their contribution as part of the team.

Pharmacy support

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 someone with pharmacy expertise. Pharmacies to be used in a trial must be assessed in the same manner as one would assess a site prior to start-up.

Remember: not all trials will need a team as described above. There may also be other team members as appropriate to the trial, for example:

- health economists (many larger funders are now requesting a health economic evaluation to be included in the trial; their time spent on the study will depend on the level of data collection but most would have input at the design/start of the study and at the end to do the economic analysis/reporting).
- social scientists.
- qualitative researchers.

Roles may be combined or on a part-time basis or seconded from elsewhere, including the host institution.

5.3 Trial identity and marketing/the trial as a business

Consider treating the trial as a business by adopting methodologies and management techniques from the business world. Francis et al.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.

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

Trial efficiency is important and the Trial Forge collaboration also has good information on recruitment and retention that should be considered at the trial start up stage. See section 6 for further information, www.trialforge.org.

Consider the following:

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

The Sponsor may need to approve any trial identity logos, etc. to ensure there is no conflict with their corporate identity. Check with the funder what they class as an "output" and what needs to be reviewed and approved before being put into the public domain (e.g. press article etc).

5.4 Standard Operating Procedures

Standard Operating Procedures (SOPs) should comprise detailed, clear and concise written instructions designed to ensure that performance of an activity is standardised, regardless of who is carrying it out. The trial Sponsor will usually expect their own SOPs to be followed, unless specified in the contracts. A number of organisations also provide example SOPs on their websites and many CTUs have core SOPs.

Topics covered include:

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

For CTIMPs, a description of the responsibilities of a trial pharmacist should be included in the trial protocol and SOPs. In addition, the Pharmacy Trial File should contain all relevant information specific to a trial, including code-breaking/unblinding procedures.

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

- Reporting pathways for adverse events.
- Monitoring and management plans.
- Data entry guidelines (details what to do if missing data/data queries etc).
- Research nurse visit guide (step by step guide for staff on what to do at each study visit).

5.5 Document development and design

Multiple documents are required to successfully conduct a clinical trial and time should be allowed to ensure that all documents are fit for purpose. The items included are not only essential documents such as the protocol, participant information leaflet and informed consent form, to name a few, but also many other documents which are needed to effectively manage a trial. These include: planning documents such as the monitoring plan and risk assessment, also independent oversight information (TSC and DMC where needed). Allow sufficient time to develop and obtain ethics approvals for the protocol and the full document set (see section 3).

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

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

Some general tips

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

The plain english campaign have useful tools for producing reader friendly documents, see www.plainenglish.co.uk/free-guides.html.

Consider other communication styles such as audio recording, videos/animations, simple language and pictures for young children. An excellent example of how animation can be used where young children are recruited into studies can be viewed at www.liverpool.ac.uk/psychology-health-and-society/departments/psychological-sciences/research/connect/resources/.

5.6 Data collection forms and management

Data collection forms or Case Report Forms (CRFs) and patient questionnaires are required in order to collect data necessary to monitor participants' progress and safety and, ultimately, for analysis of the trial end points.

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

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

- Missing data: blank answers should be avoided, especially when relating to the primary outcome. Develop forms that are clearly set out and are unambiguous in the instructions. Importantly, time spent on site training can help reduce the levels of missing data.
- Accuracy of data depends on a number of factors: training, accuracy and reliability of the data collectors; the legibility of handwriting; frequency of transcription errors when copying data or records and the accuracy of the data entry clerks.
- Validity depends on whether or not the data have been accurately recorded; the existence of a clear audit trail; recording changes to data and the reasons why will prevent the opportunity to falsify data. All changes should be initialled and dated by the person making the change.
- Yes/no options: This may not always be appropriate. Consider whether 'unknown' or 'missing' options should be included.
- Drop-down lists: these rule out the possibility of spelling errors. The preferred option for electronic systems is to have a drop-down lists, e.g. of four options, i.e. not answered, no, yes and unknown. The responses can be encoded so that it is easy to differentiate between unanswered questions and where the response is genuinely unknown.
- Free text: try to avoid free text boxes where possible as it is difficult to categorise or summarise, it can also be problematic to transcribe from paper to computer. The time taken to interpret/ analyse free text can also be vastly underestimated. Where necessary, using a coding frame to code free text as the data is accumulating will make it usable at the analysis stage. Also incorporate an automated spell-checker which includes the appropriate medical terms and medications.
- Multiple-choice questions: on paper it is straightforward to list a number of options and say 'tick one box only'. When transcribing this to an electronic system the method used often depends on how long the wording is for each option and how many options there are – too many will make the screen look cluttered.
- Some paper forms use individual boxes for each character to try to force clarity, especially for names and addresses.
- Imaging data: Where images are collected as data for the trial, perhaps for assessment of primary or secondary endpoints, it is important to consider how these will be generated, transferred, held and subsequently archived and data storage requirements and anonymisation/deidentification of images can be challenging. It may also be necessary to define what is considered source data, where the original image at a study site, cannot be retained for the life of the trial and archiving period.

Other trial forms

In CTIMPs, the Trial Manager will work closely with the Trials Pharmacist in developing and documenting the trial procedures relating to pharmacy. Typical documents produced include the dispensing procedure, drug accountability log, prescription sheet, labels and a description of the process for drug destruction.

A description of the responsibilities of the Trial Pharmacist should be included in the trial protocol and SOPs. In addition, the Pharmacy Trial File should contain all relevant information specific to a trial, including code-breaking/unblinding procedures.

5.7 Trial information system

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

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

A key strategic decision is whether to build systems in-house or to purchase an existing commercial system, for example, Inform, MACRO Electronic Data Capture (InferMed, London, UK), Rave (Medidata, New York, NY, USA), OpenClinica (Waltham, MA, USA), REDCap (powered by Vanderbilt and supported in part by the National Institutes of Health).

System design

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

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

- Computer screen design should be kept as simple as possible. Designing the screen to match the paper data collection forms will greatly enhance ease and quality of data input.
- Minimise the number of different screens needed – to avoid excessive scrolling, use tabs to move from one related section to another.
- Minimise the number of times you need to hit 'Enter' and have options to 'Save', 'Save and Continue' or 'Cancel'. Put these as action buttons at the top and bottom of each screen to minimise the need for scrolling up and down. Context-sensitive 'Help' text where necessary – a box with a '?' is standard for this.
- Put units of measurement next to the input field so users need to enter only the actual number – this can be useful in international trials where different countries may use different units.
- Drop-down lists for multiple-choice answers need less screen space than listing every choice and 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).
- Either soft or hard validation checks can be used when entering the data. Soft validation checks allow you to save the form data regardless and will show an alert if data is out-of-range; a hard validation check will not allow you to save any form data at all, meaning you will lose any out-of-range data entered.

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

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

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

the fields used and any coded values.

These will be used to create a data dictionary that will describe any exported data used for analysis.

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

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

All users must be given a unique username and password to gain access to the database and be required to give a written assurance not to share this with anyone else. Individual users are assigned roles such as data entry, data view only, which limits activity and access. 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/wp-content/uploads/2014/03/DIMS_General_Proposals_05-25-09.pdf.

5.8 Data management (Data entry checking and validation)

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

Consider the following:

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

The use of internet-based data management systems offer real-time and expedient data monitoring, which means that incorrect or ambiguous data can be corrected promptly and so improve data quality. Real-time data entry means that the Trial Manager can see an overview of activity in all sites. All data management activities should be documented in a Data Management Plan (DMP), including the processes for ensuring data is accurate and clean and should be proportionate to the trial risk assessment and monitoring plan.

Source Data

ICH-GCP defines source data as: *“all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial”*.

In essence it is where the data are first captured (either written or electronically). In order to conduct source data verification (SDV) you must be aware of what constitutes source data, therefore clear documentation must be present in the Investigator Site File about what constitute source data at the site.

Guidance from the MHRA for CTIMPs/device trials (though relevant and good practice for all trials) is 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. Many NHS trusts are also moving from paper records to electronic records only and the trial requirements should be discussed when setting up sites.

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

5.9 Data linkage

If the trial is utilising existing data sources or using data linkage services, you should allow plenty of time to set this up and ensure relevant approvals are in place. Different approvals are required dependent upon the organisation who holds the data and also vary between nations within the UK, see <https://digital.nhs.uk/services/data-access-request-service-dars/data-access-request-service-dars-process/data-access-request-service-dars-pre-application-checklist>.

5.10 Equipment

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

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

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

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

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

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

The following is a guide to the essential documents that should be in place in the TMF held at the Coordinating Centre. The ISF contains most of the essential documents that are required in the TMF. The Coordinating Centre should have an ISF contents page but examples can be found online. The NIHR have a template which can be downloaded at www.nihr.ac.uk/our-faculty/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/gcp-resources/gcp.htm.

Coordinating Centre/TMF

All trials

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

CTIMP trials

Specific information, in addition to the above, is required:

- Clinical Trial Authorisation (MHRA if in the UK) with any stated conditions addressed.
- Investigator's Brochure or Summary of Product Characteristics (SmPC).
- Pharmacy documentation/file and IMP Management plans and associated procedures.
- All records for Investigational Medicinal Products(s) procurement/supply/manufacture (e.g. shipping, QP release certificates).

5.12 Principal Investigator (PI)/site selection

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

- Be suitably qualified by education, training and experience to assume responsibility for the conduct of the trial; they should have the necessary and appropriate research experience as well as an up to date CV, health professional registration and GCP certificate.
- Have suitable facilities, including pharmacy or alternative arrangements if IMP storage, or reconstitution is required, as well as access to any specialist equipment needed and laboratory facilities.
- Have appropriate licenses/notifications/committees in place where applicable (e.g. an HTA Human

application license, Premises Notification to the HSE and/or access to a GMSC may be required in some ATIMP trials).

- Have adequate resources including appropriately qualified staff, sufficient numbers of potential participants and sufficient time to conduct the trial – take account of conflicting trials.

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

5.13 Site initiation visit/Investigators’ meeting

These may also be termed site training visits and form one of the final steps prior to starting recruitment. Before a trial starts at a site, ensure that everything is in place including approvals, essential documents and agreements and that all site staff have been trained in trial procedures and made aware of their responsibilities. The latter is achieved through a site initiation visit and/or a central investigators’ meeting. This covers a review of all documents, a review/demonstration of all procedures and confirmation of planned key dates. Documents should include a summary of the background to the trial; an overview of the protocol requirements including recruitment rate (see section 6, trial recruitment); data collection; informed consent procedure; GCP requirements; adverse event reporting; IMP storage and use; plans for monitoring visits and archiving requirements. Many Sponsors insist on a “green light form” where all crucial tasks have to be completed before the site can be open to recruitment, i.e. given the green light to start recruiting.

5.14 Investigator Site File (ISF)

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

- Final versions of documentation and copies of all relevant approval letters.
- Relevant indemnity documents.
- Final CTA (for CTIMPs).
- All pharmacy/IMP Management arrangements and documentation (CTIMPs only).
- All relevant site agreements and contracts including monetary arrangements.
- Sponsor delegation logs.
- Safety reporting/pharmacovigilance reporting procedures.
- Complete adequate training in trial procedures and GCP.
- If possible, visit the place where recruitment will take place and talk to those who will be recruiting participants.
- Discuss the trial procedures with the researchers and key people from the site to harness their experience and expertise. Involving the clinical team and gaining their support will aid recruitment.
- Agree trial logistics locally and propose ways to optimise recruitment at the site.
- Circulate approved site list.
- Agree a start date for the site.

5.15 Managing the budget

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

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

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

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

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

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

To have the best budgetary control you need to:

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

Monitor expenditure

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

Put aside a regular time to deal with financial matters each week/month. Remember always to take a global view of the funding – do not get obsessed with balance sheet accounts. Good practice would be to prepare a spreadsheet of each funding stream (if managing multiple projects) to include start dates, milestones and end dates. Develop processes to monitor spending and to check invoices.

Prepare regular financial reports. Your unit may be able to provide you with monitoring printouts for checking. Many host institutions now have online systems for managing budgets, which may avoid the need for bespoke systems. You may need the Chief Investigator to give you access to the institutional system.

Share good practice

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

Assess the trial processes on a regular basis

Consider where cost savings can be made:

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

Think ahead

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

Always

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

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

5.16 International trials

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

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

Protocol

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

Local language translations and back translations of PIS/CRFs

- is there a need for translation of the whole protocol or just the summary; are validated

Regulations

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

Indemnity arrangements

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

Ethics approvals

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

Local/national permissions

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

Safety reporting

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

Public involvement

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

Data management

- what is the role of the local trials unit?

Data protection

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

Finance

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

Drug supply

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

Clinical practice

- are there differing standards of care and protocols?

Units of measurement to be used

- check for standardisation.

Trial governance

- how to involve investigators due to time zones.

Samples for translational research or validation of study endpoints.

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

International clinical trials of ATIMPs can be particularly complex and may require specialist regulatory input. GMO approval for Gene Therapy Products follows national guidance and can be challenging and time consuming to navigate. Timelines for CTA approval can vary widely. National implementation of the EU tissues and cells legislation adds additional challenges for site set-up and in some cases product manufacture. Ensuring a thorough understanding of the national requirements around the various regulatory elements of ATIMP trials is essential.

*The EU US Privacy Shield Framework allows EU citizens' data to be transferred to/held by US companies who are active members of the Framework.

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 adding the following essential documents:

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

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

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

6.2 Trial recruitment

Recruitment strategies

Successful recruitment of the originally specified sample size to time and target is a common challenge for clinical trials and strategies to improve recruitment are subject to a wealth of research. Resources such as the ORRCA project or the Cochrane Library are available. ORRCA is a searchable database that aims to collate relevant methodological research on recruitment and may provide information on how effective a planned strategy was found to be in other trials, see www.orrca.org.uk/. The Cochrane Library is a collection of searchable databases of high-quality, independent evidence and can be used as a tool to inform decision-making in a number of areas of trial conduct, including recruitment strategies. The main Cochrane review on trial recruitment is at <http://cochranelibrary-wiley.com/doi/10.1002/14651858.MR000013.pub6/full>. Summaries of the evidence for trial recruitment strategies are also being put onto the Trial Forge website, see www.trialforge.org.

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

- How participants will be recruited.
- Where participants will be recruited.
- Who will recruit them.
- Who will provide consent; e.g. the participant (if adult with capacity) or a proxy (if a minor).
- When this will take place.

Training

As near as possible to the start of recruitment, provide training for the site staff such as Principal Investigators and research nurses, who will be responsible for recruitment. Consider whether other departments also need to be provided with training e.g. laboratory staff if a trial has non-standard sample processing, or for CTIMPs and ATIMPs pharmacy initiation may be required depending upon the nature and supply arrangements for the trial intervention/s. Training can be a group event, individual training conducted during a site initiation visit (SIV), site initiation teleconference or webinar to ensure that the appropriate team members are fully informed about the trial and their role in its conduct and delivery.

Training materials should cover procedures such as consent, safety monitoring and reporting and any trial specific arrangements for management and accountability of the trial interventions, including what should be documented, where, how and when. Spending time with site teams before they start recruiting to the trial should improve the quality of the data collected and reduce the number of data queries generated later.

Provide clear written instructions for team members. This will depend on the nature of the trial and the activity being undertaken but may take the form of a detailed Manual of Operations (MOP) or a study flowchart that clearly outlines tasks and responsibilities. A MOP facilitates communication and training within sites. A slide set can also be provided to the site for internal training of new staff. Always encourage team members to contact the Coordinating Centre 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 (mirror routine care pathways where possible).
- Plan and target marketing strategies and site visits effectively.
- Review and evaluate where possible 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:
 - ➔ personal contact
 - ➔ telephone
 - ➔ email
 - ➔ publication and letters
 - ➔ website
 - ➔ newsletters
 - ➔ webinars
 - ➔ social media

Ideas to consider to ensure optimal recruitment

- Try to understand what might make recruitment easier or more difficult and make use of this information when planning trial recruitment.
- Contact relevant voluntary organisations and charities and other patient groups for advice on how to raise awareness. Include information for these third party websites or newsletters in the ethics submission.
- Consult membership lists/networks of relevant colleges, professional organisations or disease areas.
- Place flyers in journals to encourage interested investigators.
- Attend relevant conferences to lobby opinion leaders and set up satellite meetings to promote interest.
- Produce a 'starter pack' for investigators and nurses to launch recruitment.
- Produce a list of 'frequently asked questions'.
- Consider Study Within a Trial (SWAT) initiatives so that the effects of recruitment strategies are evaluated and reported, see <https://doi.org/10.1186/s13063-018-2535-5>.

Monitoring recruitment targets

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

- set realistic targets based upon feasibility for both numbers of participants (not only number eligible but the proportion of these likely to be given the opportunity to take part and the proportion likely to give consent) and the number of sites – review regularly. Failing to hit targets is often not about poor performance but an unrealistic target.
- monitor screening activity via screening logs as these logs will give an overview of trial activity and uptake in recruiting site, identifying and enabling exploration of reasons for non-recruitment.
- change activities if necessary – monitor their impact and change things that do not work.
- be open-minded – think laterally.
- motivate site staff by reminding them about the importance of the research and potential patient benefits.
- try to factor in or pre-empt periods of low recruitment; for example, regular changes in hospital staff, holiday periods or seasonal presentation of diseases or medical conditions.
- where appropriate, advise recruiting sites to consider staggering recruitment to aid the management of timely follow-up.
- plot planned and actual recruitment (and retention) on a graph that includes future projections. This helps to see how things are going as well as highlighting whether action is needed now to address a potential future problem.

Communication strategies

- Aim to use strategies for which there is evidence of benefit, or consider running a SWAT to provide some evidence.
- Regular newsletters to all investigators: named individuals/sites who have achieved high recruitment or reached an important milestone.
- Individual feedback to sites: praise recruitment and express appreciation.
- Use social media to interact with site teams and enhance their engagement with the trial.
- Branding: relevant tokens of appreciation, mugs, post-its, pens, mouse mats, key-rings and trial-specific items have proved useful.
- Attend conferences with trial-specific literature; have an exhibition stand.
- Recruitment awards, for reaching a milestone, e.g. the 100th patient, all help to maintain interest and motivation for the trial but need to be of low value and approved by the TSC and/or funder.
- Email countdowns over the last few months of recruitment to build excitement and aid push towards the recruitment target.
- Teleconference forums.

Encourage ownership by investigators

- Publish the protocol.
- Encourage presentations by different stakeholders.
- As a group try to publish sub-studies or novel approaches, for example SWAT initiatives such as recruitment strategy evaluations, to keep trial interest high.
- Arrange meetings and attendance at conferences.
- Visit sites that are recruiting well and those that are not – learn what works and what does not.

Sites with poor recruitment

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

If recruitment is not going well, consider the following

- Is the question still relevant?
- Are there competing trials?
- Are the eligibility criteria too stringent?
- Does the trial try to engage potential participants at the wrong point in the patient pathway?
- Are investigators still interested?
- Are participants prepared to join?
- Are protocol procedures appropriate and flexible?
- Adding or closing sites – this action should be considered in the context of your understanding of barriers to recruitment. It may be that alternative strategies/corrective actions in currently open sites may improve recruitment and avoid the time and resource associated with identifying and opening new sites.

6.3 Retention and follow-up

Retention of trial participants is equally as important as recruitment of participants. If participants do not provide data they will be unable to be included in the analysis. The following list provides some areas to consider when thinking about retention of participants.

- Provide each site with a report listing due dates of follow-up and acceptable time windows. This can often be easily facilitated by bespoke reports within the trial database.
- Make sure the patient information leaflet clearly outlines what trial participation and follow-up entails. This is particularly important in the case of ATIMP trials, where follow-up may be long term for several years.
- Consider the primary outcomes of the trial and focus resources appropriately.
- Make sure all necessary permissions and appropriate consent for follow-up, such as ethics, NHS Digital are in place.
- Make sure the necessary consent and required identifiers for follow-up through central registers is obtained if there is a possibility they might be used (e.g. for longer term follow-up or if loss to follow-up).
- Organise systems and plan when the next contact with the participants should be made.

Other ideas that may be appropriate include:

- Checking systematic reviews for additional retention strategies with evidence of benefit.
- Notifying the participant by letter insert (approved by ethics committee) or text when contact is due, including reminders (e.g. if fasting is required for the study visit assessments).
- Rearranging the appointment if the participant does not respond or attend clinic.
- If appropriate to the research topic and participant population, use birthday cards, anniversary cards/Christmas cards.
- Using participant newsletters (approved by ethics committees).

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.
- obtaining data from providers of routine data, e.g. NHS digital, Information services division (Scotland) or NHS Wales informatics service. These groups hold a variety of datasets which may be able to provide you with the data you require.
- if appropriate, a shortened questionnaire including just the primary outcome data for participants reluctant to complete a full-length questionnaire.
- if appropriate, collecting primary outcome data over the telephone if the participant does not return their questionnaire.
- focusing on ensuring that follow-up at the final trial visit/final questionnaire is completed where interim visits have been missed or interim questionnaires have not been completed.

Participant questionnaire response rates

No strategies are conclusively proven to work in all trial situations, but 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 emails more personal and keeping them short; offering incentives, see *Cochrane Database Syst Rev 2009;3:MR000008, BMJ Open 2014;4:e003821. doi: 10.1136/bmjopen-2013-003821.*

6.4 Data collection and management

The trial web portal

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

6.5 Data protection – the practicalities of day-to-day management

Day-to-day management

Collect only data that is fit for purpose, approved by an ethics committee and in accordance with GDPR requirements.

- Ensure adequate security and restricted access to paper records.
- Ensure adequate security and restricted access to electronic records by use of password-protected systems on a secure network with back-up and audit trails.
- Ensure appropriate consent is obtained.
- Ensure that participants' personal information is anonymised/unlinked or pseudonymised as soon as practically possible.
- Document the reason for the timing of anonymisation of data.

Simple solutions – paper

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

Simple solutions – electronic

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

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

6.6 Monitoring

Monitoring involves overseeing the progress of the trial.

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

It may also include:

- Site monitoring visits to review the ISF and ensure that training, resources and facilities remain adequate, e.g. review of IMP storage, dispensing, accountability and review of inventories of sample storage at site.
- Source data verification during a site monitoring visit to compare data recorded on the CRF with clinical records in order to identify any errors of omission or inaccuracies. This usually concentrates on key data such as eligibility criteria, adverse events and primary outcome 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, with a description of the findings and actions, before filing in the TMF.

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

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

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

6.7 Preparing for audit and inspection

Definition of audit

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

The audit process

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

Definition of inspection

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

The inspection process

Regulatory inspections are formal processes with legal consequences if non-compliance with the regulations is identified. The MHRA implemented a fully risk-based inspection process from October 2009. The majority of organisations conducting trials were requested to complete a periodic GCP compliance report and submit to the MHRA once every 2 years in order to inform inspection scheduling based upon level of risk, taking into consideration such things as the number of trials being conducted by an organisation, type of trial, population/s involved, trial phases, prior inspection history and any organisational changes. As of 2016 routine submission of GCP compliance reports are no longer required, though organisations may be contacted directly by the MHRA GCP Inspectorate and specifically requested to provide information.

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.

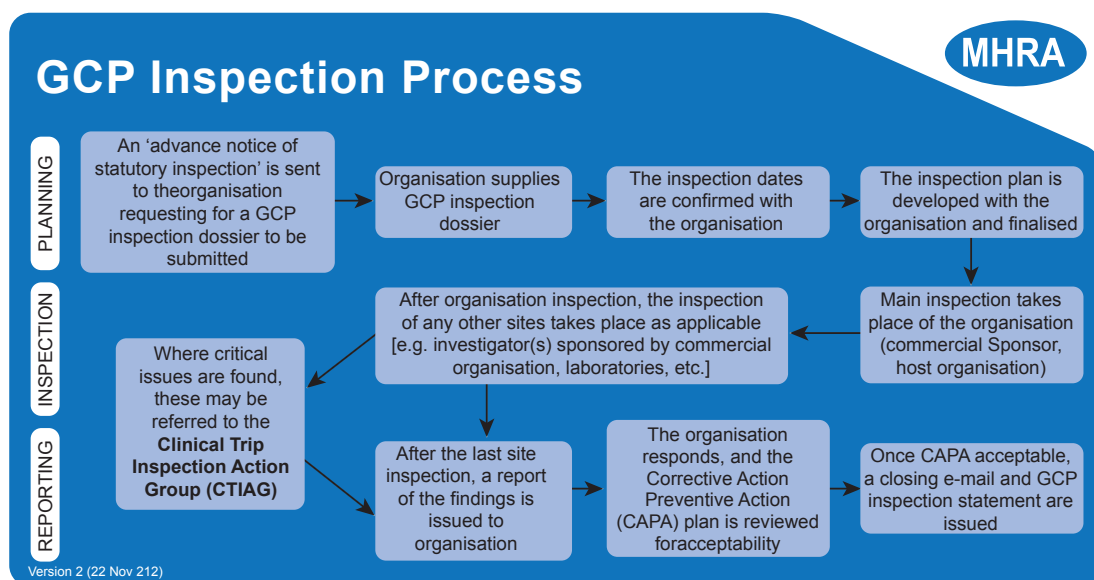
Committee for Medicinal Products for Human Use (CHMP): requested inspections resulting from central marketing authorisation submissions. The CHMP can request GCP inspections in relation to marketing applications made using the EU centralised procedure.

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?', see https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf.
- Determine who the Sponsor is for all trials and review whether older trials fall within the remit of the regulations.
- Review previous and common findings and identify areas of risk.
- Establish a work plan, prioritising important issues.
- Develop a communication plan to inform relevant internal departments and researchers as early as possible. Ensure that appropriate staff members are made aware of the need to be available for interview and that they are sufficiently prepared by holding inspection training days and mock interviews. Update training records, ensuring that they include regulatory, SOP and trial-specific training undertaken.
- Review essential documentation; ensure that all required documents, listed in ICH-GCP section 8.0.15 are present and easily located and divided into sections within the TMF or ISF.

Note: ICH-GCP does not provide a conclusive TMF contents list and depending upon the activities being undertaken additional essential documents, such as risk assessment records, should also be included in your TMF. A 'milestone summary' is useful at the front of each file. Any missing documents should be recorded on a file note, with an explanation. Access to the database if electronic data

capture is performed, or the inspectors may request a printout of eCRFs. Participants' medical notes and all completed consent forms should also be made available for review on the day of the inspection.

- Confirm that all regulatory, ethical and local approvals, including a EudraCT number for trials that commenced after 1 May 2004, were obtained prior to the trial start.
- Review document tracking and version control processes – ensure that all versions of essential documents are present and that outdated versions are clearly marked as superseded. A 'change summary' is useful for essential documents such as patient information leaflets and consent forms.
- Ensure that the staff delegation log is up-to-date, reflects the current situation and is signed by the Investigator. Signed and dated CVs should be available for all past and present staff listed on the log.
- Confirm the whereabouts of the documentation and data for any archived trials and ensure that written information from the archive site is available and that the data are stored in accordance with data protection legislation.
- Audit or monitor premises, services and trials that may be selected for inspection.
- Develop corrective and preventative action plans for any potential deficiencies identified and include a timeline for implementation.
- Ensure that notes to file are up-to-date. These may be reviewed by the MHRA during the inspection.

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

What will happen during a routine inspection?

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

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

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

What will happen after a routine inspection?

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

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

6.8 Drug management systems

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.

- If the drug/intervention is being provided by the Coordinating Centre, a distribution management system is essential. If clinical sites 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 multisite trial. All trial documentation and instructions will need to be in local languages and approved by local regulatory bodies.
- A system for independently testing a random sample of drug packs prior to distribution, especially if the Trial is placebo-controlled, should be developed to ensure the contents of numbered intervention packs match the allocation code. Using a local trials pharmacist or biochemist to carry out this testing can be cost-effective.
- A system for the destruction of unused trial drugs, during and at the close of the trial, and of any expired drugs will need to be developed early in the planning stage.
- Distribution methods need to be reliable, economical and budgeted for.
- All trial drug packs distributed will need to be accounted for at the close of the trial.

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.

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.

For ATIMP trials, the investigator should have

- a) knowledge of the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including any hazard to those handling the product and close contacts and the risk to the environment;
- b) have knowledge on the use, application, implementation or administration of the ATIMP and the requirements for clinical, efficacy and safety follow up;
- c) ensure that the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the healthcare professionals involved, are communicated to the investigator site team including the surgeons or other specialists involved.

The product may be patient specific and may be shipped directly to the investigator site rather than via pharmacy. In that case, pharmacy should be made aware of the plan to handle the product outside pharmacy and should review the arrangements for receiving, handling, storage, transport and destruction of the ATIMP. It should be documented that this review has taken place and pharmacy should confirm their agreement with arrangements for the handling of the product outside pharmacy.

Unblinding/unmasking

It is essential that there are systems in place to ensure that no unnecessary unblinding is carried out and procedures are in place for what should be done in the event of unintentional unblinding.

This helps to ensure that the integrity of the trial is protected and investigators and trial team are not influenced by knowledge of the intervention.

In general, unblinding should only be done:

- if further clinical management is dependent on the knowledge of which intervention was allocated, for example, if this information is necessary to inform ongoing medical care. This is also known as emergency blinding. If there are concerns about side effects but there is no clinical need for knowledge of the trial intervention for future management, it can be stopped or interrupted temporarily or permanently without unblinding.
- if reporting to regulators or pharma collaborators of potential SUSARs.
- at the request of the DMC.
- during any unblinded analysis as specified within the trial analysis plan.
- at the end of the trial to determine the effect of the drug/intervention.

In some circumstances it is ethical to unblind at a participant's request; for example, in a trial of a common intervention such as antibiotics, a participant may have side effects that are sufficiently serious that they do not want to be prescribed the drug again.

Ideally the randomisation codes should be held centrally by an independent unit or person, e.g. the 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, e.g. criteria for unblinding or referral process. In most cases the gate-keeper would be the trial Coordinating Centre or CTU. Ultimately, the Chief Investigator is responsible for ensuring the trial blinding and integrity is maintained. However direct access must also be provided for emergencies.

Records of ALL participants unblinded and the reason for unblinding should be kept on a confidential central system. The trial team should not have access to these data.

6.9 Safety management and reporting systems

ICH-GCP defines that “The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society”. This requirement is embodied within the first principle of the UK Policy Framework for Health and Social Care to which all research in the NHS must adhere. The trial Sponsor is responsible for safety reporting.

Ongoing safety monitoring within clinical trials is crucial if Sponsors are to meet their responsibility to promptly notify all concerned of any findings that could adversely affect the safety of research participants. The Sponsor may delegate the role of safety reporting to others e.g. the CI or a CTU, though they will remain ultimately responsible for any delegated duties, which must also be agreed in a written and signed document between all parties before the trial commences recruitment.

The HRA also provides guidance on the safety reporting requirements for research requiring UK ethical approval, see www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/. Requirements vary depending on the type of study. CTIMPs, ATIMPs or Clinical Investigations of medical devices must comply with the relevant regulatory framework with regards to safety reporting. For such trials, failure to report adverse experiences may result in regulatory, criminal and/or civil action against the Sponsor and responsible individuals.

Systems for safety reporting

Depending upon trial type (CTIMP, ATIMP, medical device or other research such as trials of surgical interventions), there are variations in the definitions applied for safety reporting, though all have their basis in ICH-GCP.

CTIMP and ATIMP trials use the definitions from the Statutory Instrument 2004/1031⁶. Additional safety reporting considerations should also be considered for ATIMP trials as laid out in Regulation (EC) No 1394/2007 and in the Human Tissue (Quality and Safety for Human Application) Regulations (SI 2007/1523)¹⁴. Clinical Investigations and trials of a CE-Marked Medical Device used for their intended purpose use the definitions based upon ISO/FDIS 14155²⁰. For other research definitions relating to safety reporting are provided by HRA. Check with the Sponsor and Funder guidance as they may have additional procedural requirements.

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

For trials evaluating a medicine/advanced therapy that falls within the scope of the UK Regulations and the EU Clinical Trials Directive, there is a need for effective and sustained input from pharmacy. Pharmacies to be used in a trial must be assessed in the same manner as one would assess a site prior to start-up. It is common for a Pharmacist to be a grant co-applicant and a member of the TMG and the Trial Manager will work closely with the Trials Pharmacist in developing and documenting. The trial procedures relating to pharmacy.

Reference Safety Information (RSI)

The RSI used for the trial should be specified in the protocol and will depend on the nature of the intervention used:

- For a CTIMP this may be the IB or SmPC. The Sponsor should select the most appropriate document.
- For an ATIMP this will be the IB.
- For a CE-marked medical device trial the manufacturer instructions for use may be used.

For other studies, the reference safety information may be detailed in the protocol or in a supplementary document e.g. in an expected adverse events list.

Reporting timelines for safety events

The trial protocol should define the timelines that have been agreed with the Sponsor for commencement and termination of safety reporting for trial participants and should take into account any applicable regulations.

For example, this could be from the point of consent to the trial, from the point of randomisation or from the point that the intervention is given and may continue to be collected for a follow-up period after the intervention is stopped based on the profile of the intervention.

In addition, SAEs whose onset occurs during a pre-randomisation period, for example during a run-in phase, may be reportable if they are a result of a protocol specified intervention or can cause the participant not to be allocated to randomised treatment, such as if hospitalisation results in a delay and renders an individual ineligible.

At each study visit, patients should be asked to provide information in relation to any Adverse Event (AE) that might have occurred since the previous visit or assessment. AEs on going at completion of the study should be followed up as required by the protocol and as clinically indicated, which is generally to resolution or stabilisation.

Notification of safety events to the Sponsor

The protocol, SOPs and delegation logs should detail reporting timelines and responsibilities. *The investigator shall notify the Sponsor of any SAEs that occurs in a subject at a trial site "immediately"*. There is no legal definition of "immediately", but this is usually defined as within 24 hours of the investigator becoming aware of the event. The Sponsor may specify in the protocol certain SAEs that an investigator does not have to notify immediately and how and when these events should be notified.

Other AEs identified in the protocol as critical to evaluations of the safety of the trial (i.e. notable events) should be reported by the investigator to the Sponsor in accordance with the requirements, including the time periods for notification, specified in the protocol.

Reporting of pregnancy

Whilst not considered to be an AE or SAE, pregnancy occurring in a trial participant (or partner of a participant) may require monitoring and follow-up as a congenital abnormality or birth defect is considered an SAE and must be included in the safety evaluation of the intervention under study.

Reporting and management of pregnancy should be considered during the risk assessment and clearly described in the protocol. Generally, any pregnancy occurring in a trial participant (or partner of a participant) should be reported to the Sponsor. The following should be considered and described in the protocol:

- Reporting procedures if pregnant women are the eligible target population for the trial.
- Whether it is necessary to follow-up pregnant partners of a male trial participant.
- How to obtain consent to follow-up a pregnancy in a trial participant or their partner (female partner of a male participant).
- How long after completion of study treatment by the trial participant (or the female partner of a male participant) to report/follow-up pregnancy.
- Whether study treatment should be stopped if pregnancy occurs. If this is not possible (e.g. in the case of an implanted medical device) describe other precautionary actions that may be required.
- Guidance about advice/counselling that should be provided to the participant/ their partner.
- Whether special obstetric care arrangements are necessary and how these will these be monitored.
- Whether follow-up of the new-born for a period post-delivery is appropriate and for how long.

Urgent Safety Measures

An urgent safety measure is a procedure not defined by the protocol, which is put in place prior to authorisation by the regulator and main REC in order to protect clinical trial participants from any immediate hazard to their health and safety. The Sponsor or investigator may take appropriate urgent safety measures and the protocol should describe how they may be implemented and notified. The main REC and the MHRA, where applicable, must be notified immediately and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

Section 7 End of Trial

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

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

7.1 Extension of end of trial

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

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

7.2 Close-out plan

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

7.3 End of the recruitment period

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

7.4 Early termination or temporary suspension of the trial

A trial can be terminated early if the TSC/DMC 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, if applicable, should be notified within 15 days of closure.

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

7.5 Planned closure Informing investigators

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

Investigators should be informed of end of trial by a letter or other suitable form of communication from the Trial Manager and/or the Chief Investigator. This should (if applicable/possible):

- thank the Investigator for their participation.
- summarise patient status – number of withdrawals, deaths, SUSARs and SAEs.
- remind the Investigator of any continuing trial obligations, e.g. updating delegation logs, informing local personnel, including the R&D Department, archiving and availability of data for queries arising after end of trial.

- arrange for the return of trial supplies and/or drug supplies.
- advise of the possibility of audit or inspection.
- outline the results of the trial or provide a copy of the trial report (if available).
- inform the investigators of the expected timing of publication.

Informing participants

Participants should be informed of the trial findings where possible. This should be discussed and agreed by the TSC. HRA guidance on informing participants is available at: www.hra.nhs.uk/planning-and-improving-research/best-practice/publication-and-dissemination-research-findings/.

Informing the Sponsor

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

Informing the Research Ethics Committee and MHRA

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

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

7.6 Site close-out

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

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

7.7 For CTIMP trials: trial drug supplies

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

7.8 Return of trial supplies that are not drugs (e.g. kits, equipment etc.)

An agreement should be made as to whether and how any trial supplies (excluding drugs) should be returned. Trial supplies may include kits or equipment e.g. centrifuges, pipettes, ECG monitors, blood sugar monitors that have been supplied to sites directly for the purposes of the trial. Unused trial supplies may need to be returned directly to the organisation that sent the supplies initially, or to the Coordinating Centre, or the agreement may state that the sites are allowed to keep the supplies for their own use once the trial has finished. The Trial Manager should ensure that sites are aware of the requirements for the end of trial and that any evidence for return of supplies is received and recorded in the TMF by the Coordinating Centre in a timely manner.

7.9 Financial closure

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

Section 8 Preparation of final reports and publication

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

8.1 Trial results

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

It is good practice to establish a publication and dissemination plan early in the trial process and ensure this is appropriately resourced. This should give consideration how best to ensure the results of the trial are translated into practice and policy and should identify the stakeholders to be informed about the trial results.

It is common practice to set up a subgroup of the TMG as a 'writing committee' who will produce initial drafts. Both the interim and the final results and subsequent reports are reviewed/approved (as appropriate) by the TMG and TSC. It is useful to outline timelines for circulating drafts for comments allowing co-authors reasonable time to respond.

For CTIMPs the Sponsor is responsible (although this responsibility can be delegated to the Coordinating Centre, as outlined in a Sponsor agreement/ delegation of responsibilities) for uploading the end of trial summary results to EudraCT as per the European Commission's guidelines¹ on posting and publication of result-related information and this is done via the CESP. There is no requirement to submit the clinical trial summary report to the MHRA; however the MHRA provides instructions on their website about how to confirm submission of the results to them.

It is important to consider the communication of the trial results to trial participants and the wider stakeholders. The Health Foundation have created a toolkit to help researchers plan for the communication of results and is available on their website, see www.health.org.uk/collection/communications-health-research-toolkit.

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

Trial registries and relevant research databases should be updated with the results, for example, the ISRCTN and UK Clinical Trials Gateway.

8.2 Trial reports

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.

The exact requirements for final reports and deadlines for submission vary and the guidance given by the Sponsor/Funder should be followed. Attention should be paid to the specific requirements associated with this to allow sufficient planning and to ensure that appropriate permissions are in place, e.g. to re-use copyright material. The NIHR have created useful information for authors and is available, see www.journalslibrary.nihr.ac.uk/information-for-authors/.

Some funders may require a separate report or monograph which provides a full account of the trial. It is always good practice to refer to the Sponsor/Funder guidance for relevant details.

The ICMJE provide guidance on overlapping publications, see www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html.

A summary of the final research report should be sent to the main REC (and MHRA for CTIMPs) within 12 months, or as stipulated, of the notification of the end of the trial. There is no standard format for final reports to the REC. As a minimum, inform the REC as to 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.

8.3 Reporting to participants

Participants should be informed of the trial results. This could be by a letter, a plain English summary on the trial website, or newsletters to participants. Consideration should also be given to disseminating the results more widely, through participating sites, GP practices, national policy makers and regulatory bodies, patient groups, voluntary organisation newsletters or hospital outpatient departments. It is possible that different key messages need to be communicated to the different stakeholders and that this may vary depending on the results of the trial. It is important to publish in formats and media accessible to trial participants and stakeholders and to consider who is best placed to present the findings.

PPI input can also help to tailor the information for health care professionals and help contextualise the results. Involve the trial PPI representatives or an appropriate organisation to obtain guidance and input on how to present the information for different target populations.

It is also important to make sure there is time and resource to do this at the end of the trial. Many of the main trial team (detailed in section 5) may no longer be funded at this stage of the trial so timing of participant dissemination should be well planned at the start.

8.4 Publications

Most public funders of research require notification of any manuscripts or other research outputs, such as conference presentations and press releases, prior to publication. A copy should be submitted to the Sponsor/Funder prior to submission, taking into account the Funder's timescale for review.

The Sponsor/Funder must be appropriately acknowledged with the use of a logo and/or statement of support or disclaimer as appropriate in all outputs.

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

Most trial results will be published in journals with free and unrestricted access. This is important, to increase reach and impact of the finding. Journals will have an article processing charge associated and costs for this should be considered upfront. Check if the Sponsor/Funder or host organisation has any additional requirements to deposit publications in a specific repository.

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 according to ICH-GCP, see www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf. Essential documents include the Trial Master File, source documents and Case Report Forms. All essential documents should be archived, including essential documents held by investigators, Sponsors and others involved in the conduct of a clinical trial. This includes service departments such as pharmacy, laboratories and radiology. Documents may be paper, electronic or both.

Essential documents must be retained and archived for sufficient time to allow for audit and inspection by regulatory authorities and should be readily available upon request. In addition, funders, journals, Sponsors and host organisations will have local policies and procedures covering archiving requirements that must also be covered. There are different archiving-periods depending upon the type of trial. For non-CTIMP studies the archive time period is usually stipulated by the Sponsor and/or local SOPs.

The clinical trials regulations defining the archiving requirements for CTIMPs can be found at: www.legislation.gov.uk/ukxi/2006/1928/regulation/18/made.

There are a number of important considerations when archiving, examples of which are listed below. For a more comprehensive list, see <https://the-hsraa.org/resources/publications/good-clinical-practice-guide-archiving>.

9.1 Named archivist

It is good practice to have a named archivist and for CTIMPs it is a legal requirement for the Sponsor to name an individual. This role does not have to be a dedicated role and can be combined with other roles, for example in the case of electronic materials, archiving may be the responsibility of IT staff. An archivist is responsible for checking the archiving facilities are appropriate, controlling and keeping a record of access to the archive (e.g. in the form of a log), recording what is held in the archive and tracking and retrieving documents on loan from the archive. Access to archives should be restricted to authorised personnel. Any change in the ownership or location should be documented, in order to allow tracking.

9.2 Multisite trials: site documentation

The Principal Investigators are responsible for archiving essential documents at their respective sites in accordance with the requirements of the Sponsor and local requirements at the host institution. It is acceptable for the Sponsor to organise for a third party to archive the site files as long as access to these remains restricted to the investigator and/or host institution (not the Sponsor). If the Investigator is no longer able to maintain custody of their essential documents, the Sponsor should be notified so that alternative arrangements can be made.

Electronic data

Electronic data should be stored in a format that permits viewing in generic software, avoiding the need for dependence upon specific software that may not be available or accessible in the future. Appropriate back up of electronic data must be considered to mitigate against the risk of failure of storage media. A review schedule should be set up to read and test records based on a risk assessment. Access to the data must be limited and managed. Integrity controls must be in place to ensure the records cannot be altered and can only be deleted when appropriate. For disaster recovery, copies of all data must be made and kept in a separate location. A Guide to Archiving of Electronic Records by the Scientific Archivists Group is available, see <https://the-hsraa.org/resources/publications/guide-archiving-electronic-records>.

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

9.3 Destruction of essential documents

There is no requirement to delete research data if it is being held for research purposes and even personal data can be stored indefinitely if it is in the “public interest”, subject to safeguards, transparency and fairness, see Data Protection Act 2018 www.legislation.gov.uk/ukpga/2018/12/contents/enacted.

If the decision is made to delete some or all of the essential documents, reasons for destruction 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.

9.4 Archiving data for further research

Researchers need to anonymise data or get participants’ permission to disclose confidential information to other researchers if participants’ would not reasonably expect it. If sharing is for a new purpose (i.e. not what the participants have already been told) the Data Controller (which is usually the Sponsor) needs to inform participants using a GDPR compliant transparency statement, examples of which can be found on the HRA website www.hra.nhs.uk. This is not always by re-contacting the participant, for example a notice on the host institution website may be more appropriate.

Participants are always able to withdraw from a study, however, research is largely exempt from the right to erasure, so all data about a participant does not necessarily need to be deleted, if a request for erasure is received. For further information consult with your Data Protection Officer.

For more guidance on how to prepare and archive data sets to be used for further analysis, see <https://mrc.ukri.org/research/policies-and-guidance-for-researchers/data-sharing/>.

Additional sources of information (by date of publication)

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

1. Treweek S et al. Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform. <https://doi.org/10.1186/>
2. Friedman LM et al. *Fundamentals of Clinical Trials*. Springer, 2015.
3. Brueton V et al. Methods that might help to keep people in randomised trials. 2013 Cochrane systematic review and meta-analysis <http://dx.doi.org/10.1136/bmjopen-2013-003821>
4. Treweek et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open* 2013;3:e002360 doi:10.1136/bmjopen-2012-002360.
5. *Good Clinical Practice (The Gray Guide)*. Medicines and Healthcare products Regulatory Agency (MHRA) The Stationery Office 2012.
6. *MRC Ethics series*. MRC Head Office 2012.
7. Probstfield JL, Frye, RL. Strategies for Recruitment and Retention of Participants in Clinical Trials. *JAMA*. 2011;306(16):1798-1799.
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