UKTMN

Trial Managers' Network

The Guide to Efficient Trial Management

Effectively managing clinical trials

Seventh (a) Edition: 2024

The Seventh Edition (a. 2024) 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.

Contents

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Disclaimers

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

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

Devolved Nations

While most of the legislation and guidance provided in this Guide applies 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).

Summary of Changes

Edition 7a Addition of Summary of Changes, Feedback to Introduction and Section 4.3 Sustainability in clinical 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 exits 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.

Forest Stewardship Council (FTC) International non-profit organisation that promotes responsible management of the world's forests via timber certification.

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.

ORRCA Online Resource for Research in Clinical trials.

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.

Patient/Participant information leaflet/sheet (PIL/PIS) 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. PPIE includes Engagement, this is public outreach and educational activities, for example manning a stall at public event to promote clinical research.

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 wellbeing 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 sixth edition was produced in 2018, it is from this version that the current group of volunteers working in 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 also available, see https://www.tmn.ac.uk/resources/35-the-guide-to-efficient-trial-management-cancer-supplement.

Scope

The main focus is predominantly late-phase, interventional, publicly 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. The information contained in this guide is up to date at the time of going to print.

Feedback

The UKTMN Editorial Board welcome suggestions and constructive feedback to ensure the correction of any errors and the constant improvement of subsequent editions of the Guide. These can be sent to uktmn@nottingham.ac.uk.

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 standard (1) 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 intervention 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 allocation 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.

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. Allocation should be concealed i.e., the investigator and participants are ignorant of and unable to predict, the next intervention allocation.

Methods

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

Blocked (or restricted) randomization: interventions assigned randomly within blocks to ensure balanced numbers 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 participant characteristics (prognostic factors). Blocked randomisation is often used within each stratum. Stratification is not feasible for small studies or where many variables exist.

Minimisation: used when there are several key prognostic variables to balance, 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.

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)

Blinding refers to withholding information about the assigned interventions from people in the trial who may be influenced by this knowledge. 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., surgeons 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. In drug trials, the placebo must be pharmacologically inactive and 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, 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. 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 (e.g., standard deviation), must be known or estimated reasonably accurately. The minimal clinically important difference should be considered when calculating the sample size. This is a difference between groups/treatments considered realistic or important by one or more key stakeholders.

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 collect primary outcome data for, and the sample size inflated to allow for this. The trial should however be designed to minimize loss to follow-up as much as possible. The sample size provides the overall recruitment target for the trial and should be pre-specified and justified in the trial protocol.

1.6 Power

The probability of detecting a clinically important difference, 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 used to express the precision in the estimated effect size at the end of a trial. Commonly a 95% confidence interval is used; this means that if we were to repeatedly sample from the same population and obtain a confidence interval for each sample, 95% of these intervals would contain the true effect. Alternatives such as 80%, 90% and 99% may also be used. If you want more confidence that an interval contains the true value, you can 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. Lifestyle/ exercise would be an important confounding factor, as exercise may be associated independently with the outcome (BMI). In a randomised controlled trial (RCT), the random assignment of study subjects to exposure categories is done to break any links between exposure and confounders. This reduces potential for confounding by generating groups that are comparable with respect to known and unknown confounding variables (2).

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) 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. The secondary outcomes chosen should be sufficient to address all relevant aspects of the intervention, including safety, 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 to standardise the outcomes that should be measured and reported for trials in a specific disease, see https://www.comet-initiative.org (3).

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 in planning the main trial. The feasibility trial will have different endpoints from the main trial, focused on 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 endpoints 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 new drug against the current gold standard treatment usually on large patient groups. The patients have 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. 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 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 the cluster, e.g., a GP practice, school, hospital etc., not the individual, as that is how the interventions would be delivered in practice. 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.

Non-inferiority trials

A trial to determine whether a new intervention is not worse than an established intervention. A non-inferiority margin for the primary outcome is pre-specified to define what “not worse” means. Sample sizes are larger than studies designed to show that a new treatment is better.

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 clinical trials and other well-designed studies. Most CTUs will have expertise in the coordination of trials involving investigational medicinal products (IMPs), which must be conducted in compliance with the UK/EU legislation (4) relating to the conduct of clinical trials.

A UKCRC Registration Process was established for CTUs responsible for coordinating multi-site 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 on their capability to centrally coordinate multi-site 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 Task and Finish Groups, and Operations Groups for Policy, Trial Management, Quality Assurance, Statistics and Information Systems.

Further details about the UKCRC Registered CTU network functions, services and 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 support patients, the public and health and care organisations across England to participate in high-quality research, thereby advancing knowledge and improving care. 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 troubleshooting 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/explore-nihr/support/clinical-research-network.htm.

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 CRN is made up of 15 Local Clinical Research Networks. The CRN delivers research across 30 specialty therapy areas, at a national and local level. The NIHR Clinical Research Network Coordinating Centre manages the CRN on behalf of the Department of Health and Social Care. 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/explore-nihr/support/clinical-research-network.htm.

In Scotland, there are seven topic-specific CRNs, 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 https://www.ukcrc.org/research-infrastructure/clinical-research-networks/clinical-research-networks-in-scotland.

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 Hospital 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 https://research.hscni.net/northern-ireland-clinical-research-network.

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://healthandcareresearchwales.org.

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. The HRA ensures high-quality health and social care research that improves people's health and wellbeing, with a core purpose of protecting and promoting the interests of patients and the public in health and social care research. 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 coordinating and standardising research regulatory practice, providing independent recommendations on the processing of identifiable patient information and overseeing a range of committees and services.

HRA functions apply to research undertaken in England, but their established partnerships with the Devolved Administrations of Scotland, Wales and Northern Ireland provide UK-wide systems, including a UK-wide Research Ethics Service and the four nations NHS and Health and Social Care (HSC) compatibility programme.

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

2.5 NIHR Research Support Service (RSS)

The NIHR Research Support Service (RSS) in England will replace the current NIHR Research Design Service (RDS) and NIHR Clinical Trials Units (CTUs) schemes when their contracts end in September 2023. The aim of the NIHR RSS scheme is to provide an integrated research design, development, collaboration and implementation system with centres that can provide seamless support from pre-application through to post-application phases for all researchers (NIHR- and non-NIHR funded) working across the remit of the NIHR. Researchers will be able to access the methodological advice and support they require, from the initial research idea to the final research outcomes. The funded centres will operate to ensure a collaborative community is established to deliver the best advice and support to each researcher, regardless of their location; to coordinate the identification of research methodology needs; and to share best practice.

The NIHR website provides up-to-date information, see https://www.nihr.ac.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 their 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	Guidelines for Good Clinical Practice (GCP) (4) https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials	Health Research Authority (HRA) www.hra.nhs.uk
	UK Policy Framework for Health and Social Care Research 2017 (5) https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research	NHS Permissions (NHS/ HSC R&D offices) https://rdforum.nhs.uk/rd-contacts-directory/
	Data Protection Act 2018 (6) https://www.legislation.gov.uk/ukpga/2018/12	Research Ethics Committee Approval https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/
	Freedom of Information Act 2000 (7) Freedom of Information Act 2000 (legislation.gov.uk)	Confidentiality Advisory Group (CAG) https://www.hra.nhs.uk/about-us/committees-and-services/confidentiality-advisory-group
In addition, for clinical trials of medicinal products	Medicines for Human Use (Clinical Trials) Regulations 2004 (8) and amendments; 2006a (9), 2006b (10), 2008 (11), and 2019 (12). The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (13). The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009 (14).	Clinical trial authorisation (CTA) from UK Competent Authority, Medicines and Healthcare products Regulatory Agency (MHRA) https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk
In addition, for clinical trials of medical devices (Trials of non-	Medicines and Medical Devices Act 2021 (15) The Medical Devices Regulations 2002 (16) and numerous amendments to this legislation including 2003 (17), 2007 (18), 2008 (11),	The HRA is working with the Medicines Healthcare products Regulatory Agency (MHRA) to develop a new coordinated assessment, which will streamline the

	Key legislation and guidance	Required approvals
CE-marked medical devices and CE-marked medical devices used for new indications).	2012 (19) and The Medical Devices (Amendment) (EU Exit) Regulations 2021 (20)	review of clinical investigations involving medical devices. Further information is available on https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device#coordinated-assessment-pathway-pilot
In addition, for clinical trials of advanced therapy investigational medicinal products	Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products (21) The Human Tissue (Quality and Safety for Human Application) Regulations 2007 (SI 2007 No.1523) and Amendments 2014 (SI 2014 No.2883), 2018 (SI 2018 No.335), EU Exit Regulations 2019 (SI 2019 No.481) and 2020 (SI 2020 No.1306) Genetically Modified Organism (Contained Use) Regulation 2014 (SI 2014 No.1663) Genetically Modified Organism (Deliberate Release) Regulation 2002 (SI 2002 2443) and amendments	Local Genetic Modification Safety Committee (GMSC) review and opinion of risk assessment for GMOs. Notification to Health and Safety Executive (HSE) for first time use of GMO at premises and/or class 2/3/4 product activities https://www.hse.gov.uk/biosafety/gmo/notifications
Depending on the specifics of a trial, the following legislation may apply, and additional approvals may be required.	Research involving participants lacking mental capacity must comply with Mental Capacity Act 2005 and amendments. See HRA website for more detail (22) https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/mental-capacity-act/ Please note under Section 30 of the MCA, CTIMPS are specifically excluded from the research provisions of the Act. This is because separate provision is made for including adults lacking capacity in CTIMPs in Schedule 1 of the Medicines for Human Use (Clinical Trials) Regulations 2004.	Any REC may approve research under the Mental Capacity Act, however, it is recommended to use RECs that have been flagged as specialists in this area.
	UK legislation that applies to the collection of Human Tissue: Human Tissue Act 2004 (23) and amendments	Human Tissue Authority https://www.hta.gov.uk
		Administration of Radioactive Substances Advisory Committee https://www.gov.uk/government/organisations/administration-of-radioactive-substances-advisory-committee

	Key legislation and guidance	Required approvals
	Gene therapy medicinal products are defined in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC)	Gene Therapy Advisory Committee https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/gene-therapy-advisory-committee
		Ministry of Defence Research Ethics Committee https://www.gov.uk/government/groups/ministry-of-defence-research-ethics-committees
		Social Care Research Ethics Committee https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/social-care-research
	The Commission on Human Medicines advises on the safety, quality and efficacy of human medicinal products. Details are set out in the Human Medicines Regulations 2012 (SI 2012/1916).	Commission on Human Medicines (CHM) including its Expert Advisory Groups (EAGs) https://www.gov.uk/government/organisations/commission-on-human-medicines
	Conducting Research in Prisons, Probation or HMPPS Headquarters	HM Prison and Probation Service (HMPPS) https://www.gov.uk/government/organisations/hm-prison-and-probation-service/about/research

UK Policy Framework for Health and Social Care Research

The UK Policy Framework for Health and Social Care Research (5) 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 2004 (8) and the EU Directive on Good Clinical Practice (4) are a legal obligation in the UK/Europe; for non CTIMPs equivalent standards set out by the Medical Research Council are acknowledged as good practice. ICH-GCP (24) 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 (6) is 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).

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 has 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 2000 (7) 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 https://ico.org.uk.

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

The Mental Capacity Act 2005 (22) is relevant to research involving adults over the age of 16 years in England and Wales. In Scotland, the Adults with Incapacity (Scotland) Act 2000 applies (25). There is no specific legislation in Northern Ireland; however, there is the common law of consent. The Mental Capacity Act does not apply to CTIMPs. The Medicines for Human Use (Clinical Trials) Regulations 2004 (8) make legal provision for participation in CTIMPs by adults lacking the capacity to consent and the endurance of consent after the loss of capacity.

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 2004 (23) came into force on 1 September 2006 and it is a statutory framework for dealing with issues relating to whole body donation and the removal, storage and use of human organs, tissue and anything containing human cells, including for research purposes. Consent from the donor or nominated representative is the fundamental principle of the Human Tissue Act.

There is separate legislation in Scotland: the Human Tissue (Scotland) Act 2006 (26). 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 at https://www.hta.gov.uk.

Clinical Trials of Investigational Medicinal Products (CTIMPs)

The EU Clinical Trials Directive (2001/20/EC) (27) 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) (8).

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

More information and advice is available, see

- MHRA website
- EudraLex website
- 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

EudraCT

EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) is the database for all interventional clinical trials on medicinal products submitted to the National Competent Authorities (NCAs) of the European Union (EU)/European Economic Area (EEA) from 1 May 2004 until 30 January 2023 under Directive 2001/20/EC, as well as for all trials conducted outside of the EEA that are part of a Paediatric Investigation Plan (PIP) and/or are conducted under Article 45 or 46 of Regulation (EC) No 1901/2006. Most of the protocol and results information of EudraCT trials is made publicly available through the European Union Clinical Trials Register.

As of 31 January 2023, all initial clinical trial applications in the European Union (EU)/European Economic Area (EEA) must be submitted through the Clinical Trials Information System (CTIS). https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system.

The EudraCT step-by-step guide, the use of the EudraCT database is now limited to:

- the performance of amendments to EU/EEA Clinical Trial Applications for which the initial submission was done before 31 January 2023
- the upload of third country files of trials conducted exclusively outside of the EU/EEA that are part of a Paediatric Investigation Plan (PIP) and/or in scope of Article 46 of the Paediatric Regulation (EC) 1901/2006 (so called “third country files”)
- the update of EudraCT trial statuses by National Competent Authorities
- the submission of results of EudraCT trials by sponsors

Sponsors must transition their trials to CTIS in case:

- their EudraCT trial is going to be conducted in additional EU/EEA member state(s), to which a EudraCT CTA was not submitted before 31 January 2023 (this is considered a new trial application for this member state)
- their EudraCT trial completion date is expected to be after 30 January 2025

In case of a multi-country trial, sponsors should ensure the harmonisation of their clinical trial under the Directive through EudraCT, prior to transitioning their trial to CTIS. For further information see https://eudract.ema.europa.eu.

Clinical Trials of Investigational Medicinal Products (CTIMPs) New Regulation

The EU legislation for clinical trials has changed. The EU Clinical Trials Regulation (No 536/2014) on clinical trials of medicinal products for human use came into application on January 31, 2022. This regulation (named the CT Regulation) establishes a new set of harmonised rules applicable to clinical trials performed in the European Union (EU) and the European Economic Area (EEA). The CT Regulation

(EU) No 536/2014 repeals the CT Directive 2001/20/EC. As a regulation, the CT Regulation is binding in its entirety on all EU countries without needing to be transposed into national law. 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.

The CT Regulation (EU) No 536/2014 foresees a 3-year transition period to CTIS. During the first year, sponsors can choose for themselves whether to apply to start a clinical trial via the new CTIS or under legacy methods (e.g., EudraCT) under the CT Directive 2001/20/EC. After the first transition year (from January 31, 2023), all new clinical trial applications must be submitted through CTIS. After the third transition year (by January 2025), all ongoing trials must be migrated to CTIS.

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 (21).

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/heafth//sites/heafth/files/files/https://health.ec.europa.eu/medicinal-products/advanced-therapies_en.

The Human Tissue (Quality and Safety) Regulations 2007 (28) 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/guidance-professionals/guidance-sector/human-application

The Genetically Modified Organism (GMO) (Contained Use) Regulations 2014 (29) 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 2002 (16) and the Medical Device (amendment) Regulations 2003 (17), 2007 (18), 2008 (11), 2012 (19) and EU Exit Regulations 2021 (20). In the UK, medicines and medical devices are regulated by the MHRA and detailed guidance can be found on the MHRA website. In addition to the UK regulations, internationally accepted documents and guidelines, such as ISO 14155 (30), should be adhered to in order to guarantee a high standard of quality.

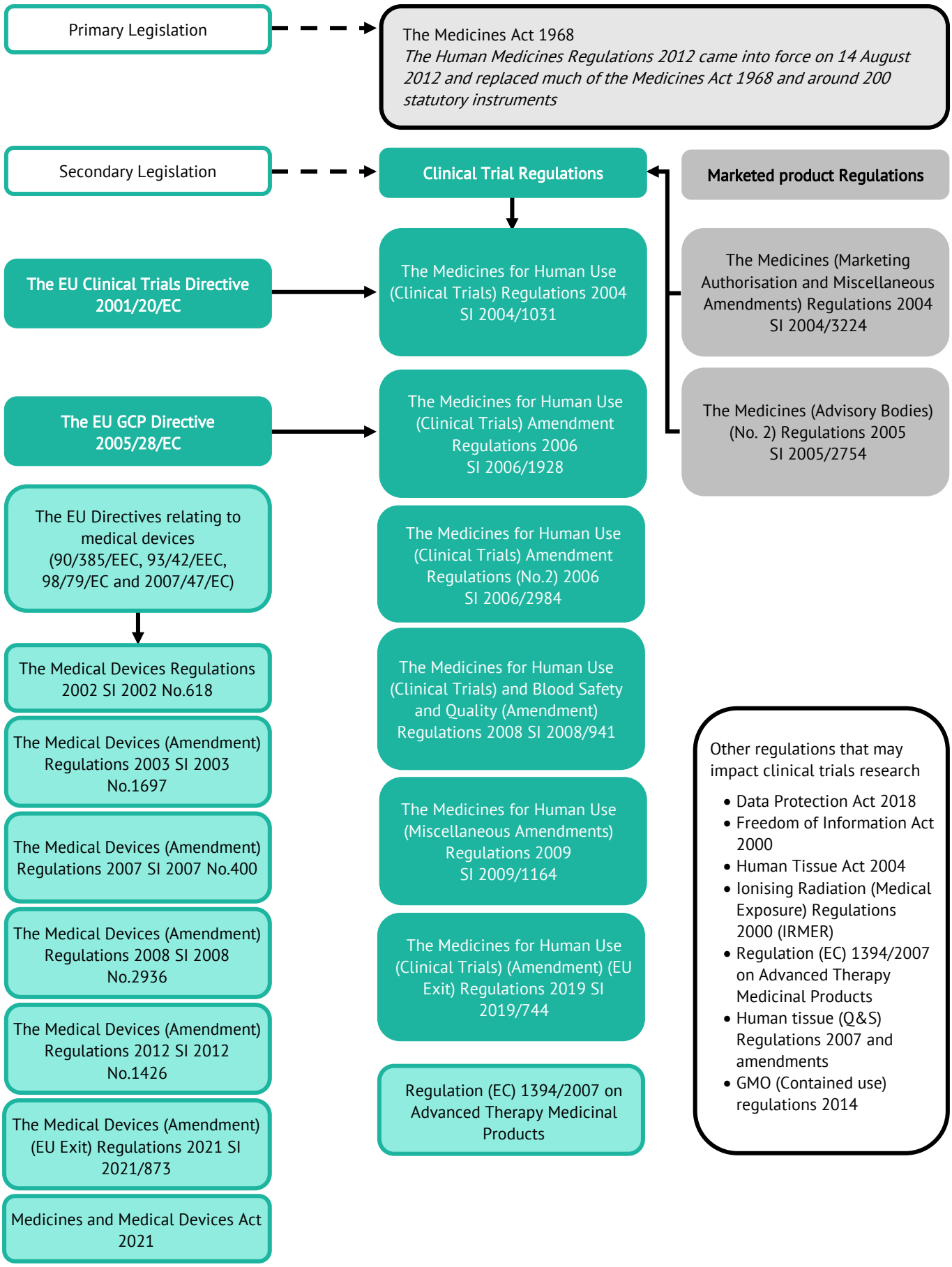
For further information, see MHRA https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency and International Organization for Standardization https://www.iso.org.

IRMER Regulations

The UK Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER) (31) 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 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).

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

Approval/Registration	All trials	CTIMP	Non CE Marked
Health Research Authority & Research Ethics Approval	Yes	Yes	Yes
Clinical Trial Authorisation (MHRA)		Yes	Yes
Registration in public registry	Yes	Yes	Yes
NHS Permission	Yes	Yes	Yes

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 (8) 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. Since leaving the EU, under proposed UK revisions to clinical trial regulations, a EudraCT number may no longer be required; at the time of writing a EudraCT number should still be obtained for CTIMP trials however no registry entry will appear for UK only trials.

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 www.isrctn.com, and ClinicalTrials.Gov 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.

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) (https://www.gov.uk/government/organisations/administration-of-radioactive-substances-advisory-committee) and the MHRA (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency) amongst others.

IRAS was recently updated following the introduction of Combined Review for new Clinical Trials of Investigational Medicinal Products (CTIMPs) and combined medicine and device trials. This process sends the application to both MHRA and REC at the same time, thereby streamlining the approval process https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot.

The previous IRAS is still available for trials approved before the introduction of Combined Review, and for research that only requires HRA/REC approval https://www.myresearchproject.org.uk.

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 https://www.hra.nhs.uk/planning-and-improving-research/best-practice/nhs-site-set-up-in-england and for Welsh led https://healthandcareresearchwales.org.

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 Participant (or Patient) Information Sheet (or Leaflet) (PIS or PIL) and informed consent form (ICF), 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 PIS and ICF so checking the policy of the registry at the time these documents 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 research (32).

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 https://www.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:

Risk analysis and mitigation

- 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 and potential mitigations considered.

Resource and timeline management

- Determining the work required and developing a schedule with milestones, i.e. identifying what needs to be achieved by what timepoint. A simplified Gantt chart may be useful to show projected timelines, 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 and quality assurance

- 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.

Communication and teamwork

- Maintaining good communication with all relevant parties.
- 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 which is usually followed by a grant or funding application. There are several places to obtain advice and support for developing trial grant applications. It is very important to have Patient and Public Involvement and Engagement (PPIE) at this stage. It is good practice to have a PPIE – co-applicant (if feasible) and PPIE involvement throughout the life cycle of the trial.

Trial design support

The NIHR Research Support Service (RSS) in England will replace the current NIHR Research Design Service (RDS) and NIHR Clinical Trials Units (CTUs) schemes when their contracts end in September 2023. The aim of the NIHR RSS scheme is to provide an integrated research design, development, collaboration and implementation system with centres that can provide seamless support from pre-application through to post-application phases for all researchers (NIHR- and non-NIHR funded) working across the remit of the NIHR. Researchers will be able to access the methodological advice

and support they require, from the initial research idea to the final research outcomes. The funded centres will operate to ensure a collaborative community is established to deliver the best advice and support to each researcher, regardless of their location; to coordinate the identification of research methodology needs; and to share best practice.

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. Early engagement with a CTU providing support is very important. 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 at https://ukcrc-ctu.org.uk/registered-ctus.

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. It is also important to consider PPIE perspectives, see https://involve.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, public involvement plans, dissemination plans and data sharing intentions. In addition, applications will need to include details of co-applicants' CVs and costs, as well as costs for PPIE. 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.

Resources and Costing

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.

Many funders now require a completed Schedule of Events Cost Attribution Template (SoECAT, https://www.nihr.ac.uk/documents/online-soecat-guidance/30396) at the point of full grant submission which has been validated by the lead NIHR Clinical Research Network (CRN); this acts as evidence to the funder that all associated NHS costs have been considered and appropriately costed against the schedule of events, and reduces the risk of unexpected and unfunded costs being discovered later in trial setup.

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.

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, monitoring, 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 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 will have access to tools within their institution to accurately calculate costs according to university and funder requirements. 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, and 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. Depending on the funder these staffing costs may also include additional contributions such as indirect or estates costs.
- IMP/intervention/device costs including drug/placebo manufacture, labelling, blinding, device or intervention purchase, testing, storage, shipping and destruction and unblinding arrangements.
- Equipment purchase, testing and delivery e.g., centrifuges, freezers, monitors.
- MHRA fees for initial submission, amendments and annual safety reporting for CTIMP and device trials.
- Laboratory or other test fees for translational outcomes; 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.
- Media costs (infographics, videos for recruitment etc)
- 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 validated 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, pharmacy, consumables, 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 (such as the SoECAT). 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 patients in your trial can help to improve the quality, relevance and acceptability of the trial to potential trial participants. INVOLVE was a national advisory body funded by the NIHR that lead to the advancement of public involvement in NHS, public health and social care research in the UK and beyond. INVOLVE was dissolved in 2020 and was subsequently incorporated into the NIHR Centre for Engagement and Dissemination which includes Be Part of Research, which encourages patients to participate in clinical research https://bepartofresearch.nihr.ac.uk.

Public involvement in research is 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, https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/what-do-i-need-do.

To help plan public involvement in a trial, the following points should be considered:

- 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.
- Establishing and maintaining good communications is vital for successful involvement and this ties into the advice above 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.
- 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, at a departmental level or approaching disease specific charities.
- 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, consider different options for recruitment. For example, is a 'formal' interview the best approach — is it likely to identify the best people for the role?
- 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.
- Trials are complicated so people need to be well supported. 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. Over a programme of research, more experienced PPIE representatives may be able to take on a mentoring role with newer members.
- 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.
- 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.

It is important that PPIE representatives are appropriately compensated for their valuable contribution to clinical research. At a minimum any reasonable expenses incurred as part of the research activity should be reimbursed, so appropriate funding should be budgeted for in the trial funding application. Further guidance on recommended fees can be found at https://www.nihr.ac.uk/documents/payment-guidance-for-members-of-the-public-considering-involvement-in-research/27372.

More information, guidance and standards for public involvement can be found on the Involve Patients section of the HRA website, which provides links to many useful resources https://www.nihr.ac.uk/health-and-care-professionals/engagement-and-participation-in-research/involve-patients.htm.

4.3 Sustainability in clinical trials

Given that we are heading towards multiple climate tipping points and clinical trials contribute substantially to greenhouse gas emissions, we must all avoid doing trials that do not need to be done and begin to consider the environment in the design and delivery of trials that do need to be done. One resource developed to help health researchers do this through sensible study design are the NIHR Carbon reduction guidelines, see NIHR Carbon Reduction Guidelines for their recommendations and more information. In addition to this, The Low Carbon Clinical Trials group have published an editorial which sets out a strategy to reduce the carbon footprint of clinical trials (33). An NIHR-funded project is currently underway, which aims to develop a method and guidance for estimating the carbon footprint of clinical trials to inform future lower carbon trial design, see https://shcoalition.org/clinical-trials for more information. The method will be published on completion of the project for use by the academic trial community.

To date, the few studies on the carbon footprint of clinical trials have identified CTUs building emissions, distribution/deliveries, and trial-related travel as the main contributors (34). An assessment of 12 pragmatic RCTs showed that the average CO_2 emissions generated was 78.4 (range 42.1-112.7) tonnes, which is equivalent to that produced in one year by approximately nine people in the United Kingdom (35). Although this study did not assess building emissions, it found that trial team commuting/travel and study sites' fuel use were the leading contributors to their carbon footprint. Finally, lighter trial materials and web-based data entry contributed to the lower emissions of the CRASH-2 trial compared with the CRASH-1 trial (36).

Pending further data, we encourage you to make responsible research decisions to reduce the potential carbon footprint of different activities in trial design and delivery, following the NIHR Carbon Reduction Guidelines and the information above about the main sources of emissions. Pragmatic examples of this could be to:

- Reduce carbon emissions from travel by opting for virtual meetings and considering more sustainable modes of transport, for example replacing driving and short-haul flights with public transport and trains.
- Consider how monitoring practices can be made more sustainable, for example through remote monitoring, local monitors, more sustainable modes of transport and reducing overnight stays.
- Reduce emissions attributed to in person patient visits where possible and appropriate, for example by permitting virtual appointments where conducted in routine practice, carefully considering where additional in-person trial visits can be reduced or combined, allowing e-completion of consent or patient questionnaires where possible, or permitting routine procedures to be carried out at facilities geographically closer to the patient.
- Reduce unnecessary shipments to participating sites for example by, where possible, only shipping IMP and supplies to sites when they have identified potential patients.
- Move from a paper to an electronic Trial Master File.
- Reduce printing, especially of emails, and switching to sustainable paper choices, e.g., Forest Stewardship Council (FSC) certified.
- Ensure you are aware of and comply with any strategies or targets your institution has implemented to reduce carbon emissions.

4.4 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:

- 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 (37) (A - testing authorised medicinal products in accordance with the marketing authorisation, B - testing authorised medicinal products according to treatment regimens outside the marketing authorisation, or C - testing non-authorised medicinal products) 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. Consider the impact of any changes to the risk assessment on other trial documents (e.g. protocol, PIS/PIL). If no changes are required, evidence that the review has taken place should be filed in the TMF.

4.5 Trial protocol

The trial protocol is the document that describes the scientific idea, the hypothesis to be evaluated and the operational procedures, so it 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 ensuring all members of the team are aware of and in agreement with this 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 sub-study papers prior to the main trial publications. It should be noted that many funders will require notification (and possibly approval, particularly for commercially funded or sponsored studies) of any publications arising from their funding.

Further considerations for the dissemination of the trial results to the patient and public audience should be made during trial setup in consultation with PPI representatives, as discussed earlier in this chapter. This is a requirement of many funders and an expectation of regulatory authorities.

4.6 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.

4.7 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. All meetings should follow a set agenda and formal minutes should be recorded in addition to action points or issues arising that require action from the group. The TMG is usually chaired by the CI or another senior investigator.

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, either face-to-face or via video/teleconference. 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, whilst detailing the responsibilities of members. All members are required to sign the charter and declare any potential conflicts of interest. Recommendations for the content of a DMC charter were described by the DAMOCLES Study Group in 2005 (38), and now form the basis of most DMC charters.

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. In these cases where the TSC takes on the additional responsibility of considering safety data, this may be referred to as a Trial Safety Committee (TSC) or Study Review Committee (SRC).

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.

4.8 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. For CTIMPs that have received funding or IMP in kind from a pharmaceutical company, they will often request regular progress reports and operational meetings.

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 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 officially begins once the grant has been awarded and is a very busy and complex stage of a trial with 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. The set-up phase can take many months and the workload should never be under-estimated. The planned start date for the trial must be realistically discussed among the study management group.

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 comprise:

- A team or individual who is part of a dedicated CTU.
- A team or individual who reside(s) in a clinical department in a hospital or GP practice.
- A team or individual who reside(s) in an academic department in a university.
- A team which is split over different locations and comprise of any 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, health economics 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 any aspect of the trial. The coordinating centre will usually host the systems for data management, administration, finance and personnel management.

Remember the trial may grow and additional staff may be required as the trial progresses however, a typical Coordinating Centre trial team can consist of the following:

- Chief Investigator(s)
- Trial Manager
- Administrative support
- IT Programmer support
- Database Manager and/or Data Assistant/Data coordinator
- Statistician
- Health Economist
- Qualitative Researcher
- Methodologist
- 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%, 0.5 full time equivalent (FTE) of an IT programmer. The functions, responsibilities, competencies required and predicted workload should be incorporated 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 as this title specifically relates to legal responsibilities specified in UK and international laws.

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 who is 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 multi-talented with good leadership skills, hard-working, well organised with an ability to multi-task, capable of decision-making and excellent communicators. Further details of the competencies required to be a trial manager can be found at https://www.tmn.ac.uk/resources/73-competency-framework-for-trial-management.

Administrative support

This is a key support role with varying responsibilities and titles, such as 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) and is 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 software (for example Electronic Data Capture systems (EDC)) 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 software 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/EDC 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. The Data Manager (along with other crucial members of the trial team) would be responsible for drafting the study data management plan (see section 5.8 for further information).

Data Assistant/Data Coordinator

The Data Assistant/Coordinator focus should be trial data processing and quality. Ensuring timely data collection activities are performed such as sending out data collection forms, checking the data is collected and any data queries raised in the EDC are returned for correction by site staff are key tasks. This is a crucial role as accurate and complete data is essential. The Data assistant role can also include other office duties, such as filing, issuing GP letters and study questionnaires.

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. A trial will rarely need full-time statistical support as the statistician's 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 to answer the research question/ outcomes 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. They

may also act as a link to wider patient/public audiences to include broader, more diverse perspectives which inform recruitment and/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. Further details about patient and public involvement can be found at PPI (Patient and Public Involvement) resources for applicants to NIHR research programmes | NIHR and Patient and Public Involvement (PPI) - Research Design Service South Central (nihr.ac.uk). 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. It is important to maintain contact with the patient and public members throughout the lifetime of the trial and to discuss with them how this can be achieved. Early conversations with the host institution's funding office on how their time will be reimbursed should be undertaken in order that there is hassle free payment.

Pharmacy support

For trials evaluating a medicine that falls within the scope of the UK Regulations and the EU Clinical Trials Directive, further information can be found here Clinical trials in human medicines | European Medicines Agency (europa.eu), but please be aware that the guidance is constantly evolving so double check you have the latest version. For these trials there is a need for effective and sustained input from someone with pharmacy expertise. Pharmacies used in trials 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 economist (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, including helping with the design of data collection tools and at the end to do the economic analysis/reporting).
- social scientist.
- qualitative researcher (larger funders may also request elements of process evaluation is included in trials, often supporting pilot phases with early recruitment to identify barriers and facilitators to successful recruitment with site staff and the trial participant population).

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.* (39) 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 (See chapter 6 for more information on inclusivity). The trial needs to be promoted both to ensure that it is at the forefront of investigators' minds and also to engage with participants, potential participants and other stakeholders. 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 chapter 6, for further information, www.trialforge.org.

Consider the following:

- Aim to give the trial an individual identity; the name, acronym and logo that is both 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 input.
- Consider using 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. The time and commitment involved in maintaining a social media presence should not be underestimated.
- Use the trial identity on all customised stationery, data forms and other promotional materials.
- Set up dedicated telephone lines, answering 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, social media 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 may 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.
- Reporting deviations.
- 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, if applicable.

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) or guidance documents 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 Sponsor, host institution or the trial coordinating centre 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.

Documents required are not only ***essential*** documents such as the protocol, participant/patient information leaflet/sheet 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 which can include charters and report templates (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).

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 and should have relevant PPI input. 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, seeking PPI input (if appropriate) 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 has useful tools for producing reader friendly documents, see http://plainenglish.co.uk.

Consider other communication styles such as audio recording, videos/animations, simple language and pictures for young children, or people with learning difficulties, etc.

5.6 Data collection forms and management

Data collection forms or Case Report Forms (CRFs) and patient questionnaires are required 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. Data collection should be efficient. Do not collect data "just in case". Collect data that is necessary to answer the research questions.

Forms can be paper or electronic and should be developed with the Chief Investigator, Trial Manager, IT Programmer, Statistician, Health Economist and data team. Do not underestimate the time this process can take. There are some important points to note when developing them:

- Take care to record all versions (number and date) in chronological order.
- Missing data: unanswered questions should be avoided, especially when relating to the primary outcome. Develop forms that are clearly set out and are unambiguous in the instructions. Add n/a (or similar) to the response options to avoid people missing the question out if it is not relevant to them 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 made using a controlled correction (change initialled and dated by the person making the change). An appropriate change record should be available if data is collected electronically also.
- Yes/no options: This may not always be appropriate or inclusive. Consider whether 'unknown' or 'missing' options should be included.
- Drop-down lists: these rule out the possibility of spelling errors. One option for electronic systems is to have a drop-down list, 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 is at a study site, and 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.

In clinical investigations for medical devices, the Trial Manager will work closely with the device manufacturer to develop the trial procedures relating to the device. Documentation that requires development is likely to differ depending on the device under investigation.

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 or EDC software. 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 and follow-up questionnaires, 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. Computer Systems Validation (CSV) 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, Oracle 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. Take care to record all versions (number and date) of this systems document in chronological order so the evolution of the system is clearly traceable.

The key component of the system is the data entry and management tool, often referred to as the 'trial database' or EDC. 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, or allow the option to select the appropriate unit to avoid the need to convert data at site.
- 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 /branching logic 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 acceptance testing, end to end 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 onto the trial database. 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 may 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 key members of the trial team i.e., the Trial Manager, Data Manager, Statistician, Health Economist, Chief Investigator

etc. 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)

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. The use of digital systems provide more capability to identify and query out-of-range or invalid data at the point of entry. EDC 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 EDC 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 (e.g., BMI - calculated from height and weight values).
- 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 offers 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 remotely monitor data collection at sites.

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 digital 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 is 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 funding is available and approvals are in place. Different approvals and applications 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, laptop computers, mobile phones, scanners, dedicated internal computer network and laboratory equipment.
- The host institution should provide the basics - desks, chairs, lighting and telephones, however, this is not guaranteed so worth checking what will be made available.
- 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.

Seek advice also on the procurement of other trial supplies (e.g. drug placebo, devices, other equipment) if required. Consideration should be given to

- Organisational procurement policies may vary depending on the items or value of items required.
- Timelines for procurement (e.g., if EU tender is required)
- Timelines for manufacture
- Expiry

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

A TMF containing all the essential documents to conduct the trial should be set up at the beginning of the trial but maintained throughout by the trial team. 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 and Device trials) 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.

Coordinating Centre/TMF

All trials

- Confirmation of Sponsorship letter.
- Final approved trial protocol signed by all parties according to local requirements.
- Final approved Clinical Investigation Plan (Clinical investigations of medical devices) 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 facing documents 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/ Organisation Information Document/ site agreement (if applicable).
- Local NHS permission (confirmation of local capacity and capability/R&D approval
- Final approved risk assessment document and any monitoring plan.
- 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.
- Charters for data monitoring committee or trial steering or management group
- 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 study team members.
- Normal values/ranges for laboratory/medical/technical tests/procedures.
- Laboratory accreditation(s), range values and maintenance logs.
- 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. For further information about the MHRA Combined review go to Clinical trials for medicines: apply for authorisation in the UK - GOV.UK (www.gov.uk).
- 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).

Clinical investigations of medical devices trials

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

- Clinical Trial Authorisation (MHRA if in the UK) with any stated conditions addressed.
- Clinical Investigator's Brochure.
- Instruction for use of medical device.
- All device documentation

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 at their site; they should have the necessary and appropriate research experience as well as an up-to-date CV, health professional registration and GCP certificate. In clinical investigations of medical device trials CVs for UK clinical investigators are submitted to the MHRA
- 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

Before a trial starts at a site, everything must be in place as described above. When the documents are sent to a site particularly when working with the NHS, this is referred to a Local Information Pack (LIP), Guidance about what should be included in the LIP and template emails can be found here IRAS Help - Preparing & submitting applications - Site specific information (myresearchproject.org.uk).

The final step is to ensure that all site staff have been trained in trial procedures and made aware of their responsibilities. This is achieved through a site initiation visit, a central investigators' meeting which can be held face to face or virtually, or the use of online recorded training. 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.

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.

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).
- Clinical Investigation – no objection (MHRA approval for Clinical investigation of medical device).
- All pharmacy/IMP Management arrangements and documentation (CTIMPs only).
- All device documentation (Clinical investigation of medical device only).
- All relevant site agreements and contracts including monetary arrangements.
- Sponsor delegation logs.
- Safety reporting/pharmacovigilance/device deficiency (clinical investigation of medical device) reporting procedures.
- Complete adequate training in trial procedures and GCP.
- Provide the site with all equipment/IMP required to deliver the trial.
- 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.

See section 4.1, Planning a grant application for a trial, for more background on trial funding.

For trials funded on a grant, the Chief Investigator is likely to be the main budget holder and retain responsibility for spending even when the trial manager has been given this responsibility for managing the budget.

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.
- take advice from appropriate sources.
- be transparent with your trial team.

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 financial software packages. Also, attend any courses on relevant financial management provided by the host institution.

Put aside a regular time to deal with financial matters each week/month. Develop processes to monitor spending and to check invoices. Prepare regular financial reports. Many host institutions now have online systems for managing budgets, which may avoid the need for bespoke systems.

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®, Microsoft TeamsTM, ZoomTM 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

- 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. Understand what can be vired and if permission from the funder is required before viring.
- be aware of additional funding streams.
- use economies of scale and combine processes across trials where possible.
- use technologies/lessons learned from previous trials.
- network both locally and nationally to check for special rates for printing and consumables.

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. This can be an academic institution who are experienced with conducting trials, or commercial Clinical Research Organisation (CRO). Many CTUs use the National Coordinating Centre (NCC) model whereby a coordinating centre is assigned by the sponsor in each country. The NCC acts as a central point for country specific queries and regulatory submissions. The responsibilities of the NCC, sponsor and sites will be clearly laid out in any contractual agreements. Each NCC will have a lead investigator which is delegated some responsibilities in that country of the overall trial Chief Investigator. Some NCCs can be responsible for numerous countries if the regulatory approvals and clinical trial processes are similar, an example of this European Organisation for Research and Treatment of Cancer (EORTC) who act as NCC for cancer studies in several European countries.

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?
- If specific information or additional trial procedures should be included for a specific country, consider generating a protocol appendix for that country, or allowing flexibility where possible using wording such “in accordance to local practice/regulations”.

Local language translations and back translations of trial documents

- Is there a need for translation of the whole protocol or just the summary
- Clarify whether regulatory or ethics committee needs trial documents translated
- Consider whether site staff need to be provided with trial materials in their local language
- Clarify what language(s) participant trial materials need to be translated in, e.g., Spanish translation is required in USA
- Generate a translation procedure document and include the translation process such as sign-off procedure, selection of translation vendor, requirement of back translation or a third person's validation.

Regulations

- Is there a possible requirement for an in-country Sponsor; what is the level of SDV required? Post-BREXIT, UK can no longer sponsor trials in European member states so this must be delegated to a party in a member state.
- Consider potential differences in expected PI roles and the responsibilities.

Indemnity arrangements

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

Ethics approvals

- Clarify ethics approvals system in each country. There may be central, local, or mixture of approval bodies
- Is there a requirement for payment to ethics committees?

Local/national permissions

- Are permissions required from other bodies, differing definitions of non-commercial trial?

Safety reporting

- Confirm involvement of relevant parties (e.g., site, site director, site PI, ethics committee, regulatory) in receiving safety reports; content of safety reporting (e.g., SUSAR line list); timeline
- Requirements of reporting to Eudravigilance for EU countries; timelines; reports required?

Public involvement

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

Data management

- Consider the process for the data transfer between countries and any potential obstacles (e.g., firewall issue in China)

- What is the role of the local trials' unit (if there is one)?
- Ensure structure of TMF allows capacity to accommodate required documents from multiple regions
- Check archiving period requirements in all regions as this may vary

Data protection

- Clarify permitted use of identifiers, access to clinic records, additional requirements[1]
- Need to comply with data protection regulation in each country

Finance

- Is there a requirement to reimburse sites for regular clinic appointments and assessments as well as additional visits required by the protocol?
- Is there a requirement to reimburse participants?

Drug supply

- Clarify QP (Qualified Person) release and labelling, importation procedures and taxes, local availability/provision of drug if commercial stock, lack of trial pharmacists, wider use of community pharmacists, climatic conditions
- Clarify storage conditions (e.g., required storage temperature may differ in each country)
- Consider country specific requirements for study treatment transportation (e.g., temperature control)
- Consider country specific requirements for study treatment dispensing to participants
- Consider differences for drug destruction procedure

Clinical practice

- Are there differing standards of care?
- Age of consent can differ between countries
- Qualifications of site staff may differ between countries. Considerations should be given when assigning study roles and responsibilities;
- Can trial visits be integrated with routine clinic setup.

Laboratory assessments

- Consider the standard units of measurements used in each country.
- Check local laboratory accreditation requirements;
- Check differences between QC systems in local laboratories.

[1] 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.

Trial governance

- Consider trial coordination with regional coordinating office in each region/country;
- Consider involving national representatives on the Trial Steering Committee.

Monitoring

- If different monitoring groups are utilised across regions, consider how to standardise monitoring procedures/visits (e.g., co-monitoring).

Sample and equipment import/export

- Consider restrictions and the lead times;
- Local procedures may differ.

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.

Section 6 During the trial

During the trial, several activities and processes need to be 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 must be kept up to date by adding essential documents such as the following:

- New versions of the essential documents described in Section 5; 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
- Records for any new staff
- 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 advanced therapy investigational medicinal product trial (ATIMP)
- Records of any biological samples collected
- Subject screening logs
- Source documents (ISF only)
- Signed consent forms (generally ISF only, but may be collected centrally with the consent of participants)
- Subject ID code list (ISF only)

This is not an exhaustive list (see https://tmfrefmodel.com for a reference definition of TMF content). 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. Acknowledgement of any missing documents should be recorded on a file note, with an explanation as to why they are missing. Keep the TMF index updated with file notes indicating 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 (and when those amendments 'go live' at sites) of protocol, PIS/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 (Online Resource for Recruitment research in Clinical triAls, http://www.orrca.org.uk) project or the Cochrane Library (http://www.cochranelibrary.com) 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. 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, such as recruitment strategies (40). Summaries of the evidence for trial recruitment strategies are also being put on the Trial Forge website (see www.trialforge.org).

It is important to consider equality, diversity, and inclusion in trial recruitment, and how to include under-served groups in your recruitment. The INCLUDE ethnicity framework provides worksheets to prompt trial teams to think about who should be involved as participants: see https://www.trialforge.org/trial-forge-centre/include/ and https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435 Trial Forge Guidance 3 discusses how best to recruit participants from ethnic minority backgrounds (41).

Provide clear instructions to make recruitment as simple as possible. When planning the recruitment process, always consider:

- Where participants will be recruited
- How eligible participants will be identified and approached
- 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
- What methods of consent will be used (for instance, paper, e-consent, remote consent)
- What procedures site staff will need to follow (for instance, screening, randomisation, collection of baseline data and contact details)
- Potential barriers to the recruitment of particular patient groups, e.g., language, digital poverty (if requiring electronic questionnaire completion), difficulty in attending trial visits

Training

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

Training materials should cover procedures such as consent, safety monitoring and reporting, data collection, 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), guidance sheets, or a study flowchart that clearly outlines tasks and responsibilities. These types of documents will facilitate 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 to build rapport.

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.
- Be responsive to sites. Where possible, respond quickly to queries or pass them on promptly to the relevant individual.
- Be enthusiastic.
- Make use of PPI. PPI input can help identify barriers to recruitment, troubleshoot issues, and provide advice on how to ensure optimal recruitment for your participant population.
- Try to understand what might make recruitment easier or more difficult and make use of this information when planning trial recruitment and adapt recruitment strategies based on feedback from participants/site staff.
- Use all methods of communication as appropriate to maintain regular contact with all sites:
  - ✓ face-to-face contact
  - ✓ telephone
  - ✓ email
  - ✓ publication and letters
  - ✓ website
  - ✓ newsletters
  - ✓ video calls/teleconferencing e.g. Zoom
  - ✓ webinars/online presentations
  - ✓ social media

Ideas to consider to ensure optimal recruitment

- Contact relevant voluntary organisations and charities and other patient groups for advice on how to raise awareness. Include information for these third-party websites or newsletters in the ethics submission.
- Consult your Clinical Research Network (CRN; from April 2024, the NIHR Research Delivery Network) if your trial is part of the NIHR CRN Portfolio, and thus eligible for CRN support (see https://www.nihr.ac.uk/explore-nihr/support/clinical-research-network.htm).

- 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.
- Set up a buddy system across sites.
- Optimise use of technology; for instance, using YouTube, animations, QR codes, or tablets to make information easy to take on board and data collection easy to carry out.
- Consider translation of trial documents and/or access to interpreters to ensure equality, diversity and inclusion (ask sites whether they have a large non-English-speaking population).
- Produce a list of frequently asked questions.
- Hold investigator meetings to share progress, discuss common issues and share experiences
- Consider Study Within a Trial (SWAT) initiatives so that the effects of recruitment strategies are evaluated and reported (42).
- Communication with site staff to identify recruitment barriers
- Motivate site staff by reminding them about the importance of the research and potential patient benefits.
- Use of screening logs and embedded qualitative work to improve recruitment.

Monitoring recruitment targets

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

- Set realistic targets based upon feasibility both for 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 sites, thus identifying and enabling exploration of reasons for non-recruitment.
- Change activities if necessary – monitor the impact of any amendments and change things that do not work.
- Be open-minded - think laterally.
- 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.
- Include recruitment tables and progress to regular reports to be reviewed at Trial Management Group meetings.

Communication strategies

- Aim to use strategies for which there is evidence of benefit, or consider running a SWAT to provide some evidence.
- Send regular newsletters to all investigators: update sites on trial progress, flag useful tips or potential issues, and name individuals/sites who have achieved high recruitment or reached an important milestone. Try to keep these concise to increase the likelihood that they will be read, and encourage a speedy writing and review process in-house so that recent news and achievements can be quickly circulated.
- Give individual feedback to sites: praise recruitment and express appreciation. For example, send certificates when sites get their first recruit or achieve milestones.
- Use websites and 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; have an exhibition stand with trial-specific literature.
- Provide recruitment awards, for reaching a milestone, e.g. the 100th patient; these help to maintain interest and motivation for the trial but need to be of low value and approved by the TSC and/ or funder.
- Send email countdowns over the last few months of recruitment to build excitement and aid push towards the recruitment target.
- Hold tele/videoconference forums with the PIs and/or research nurses to share ideas of best practice and troubleshoot issues.

Encourage ownership by investigators

- Publish the protocol.
- If eligible, take part in the NIHR Associate Principal Investigator (API) scheme (see https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm).
- Encourage presentations by different stakeholders at relevant conferences or within their institutions.
- 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; involve PPI representatives.
- Consider that 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 research question still relevant?
- Are there competing trials?
- Are the eligibility criteria too stringent? (Screening data and reasons for screening failures are informative here)
- Does the trial try to engage potential participants at the wrong point in the patient pathway?
- How are site staff presenting the trial to potential participants (for instance, with regard to whether one arm might be more desirable than the other)?
- Are site staff not in equipoise (that is, they feel that potential participants would benefit from one trial arm over another, and thus are not willing to randomise them)?
- Are investigators still interested?
- Are participants prepared to join? Or do they feel that taking part in the trial would be unduly burdensome (for instance, there are too many follow-up questionnaires to complete or lots of in-person clinic visits)?
- Are protocol procedures appropriate and flexible?
- Based on the answers to these questions, are there strategies that could be employed to improve recruitment?
- 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.
- Seeking input from PPI group, Co-applicant Group, Trials Steering Committee, Data Monitoring Committee and Funder as required.

6.3 Retention and follow-up

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

- Make sure all necessary permissions and appropriate consent for follow-up (for instance, 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).
- Make sure the patient information leaflet clearly outlines what trial participation and follow-up entails. This is particularly important when follow-up may be long-term for several years. Source feedback from PPI representatives on how you present this and the difficulties that participants may face in adhering to follow-up.
- Consider the aims of the trial, the population under investigation and the resources available when developing strategies to improve retention.
- Consider the primary outcomes of the trial and focus resources appropriately.
- Organise systems and plan when the next contact with the participants should be made. 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.

- Agree a process for non-responders, for instance, a system of reminders (including who will carry these out and by what method, and remembering that they require ethical approval), and when you will class a participant as lost to follow-up.
- Monitor retention as closely as recruitment; poor retention means poor data.

Other ideas that may be appropriate include:

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

If you do not get a response from the participant, 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 (may incur a fee).
- Obtaining data from providers of routine data, e.g. NHS Digital, Public Health Scotland (formerly Information Services Division (ISD) or NHS Wales Informatics Service. These groups hold a variety of datasets which may be able to provide you with the data you require. (Begin exploring this as early as possible if you think that you will require it, as sourcing such datasets can be a long process, has associated costs and required appropriate consent and approvals in place.
- 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.
- Where interim visits have been missed or interim questionnaires have not been completed, focusing on ensuring that follow-up at the final trial visit/final questionnaire is completed.

Participant questionnaire response rates

No strategies are conclusively proven to work in all trial situations, but a Cochrane Systematic Review published in 2009 (43) 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.

A further Cochrane Systematic Review in 2014 provided further support for incentives, sending by recorded delivery, and implementing a “package” of postal communication strategies (44).

Trial website and social media

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. Trial websites can be used to provide further information on a trial, thus reducing the amount of information that needs to be included in the patient documentation.

Social media may be used to raise awareness of the trial among sites, clinicians, academics, policymakers, and, in some cases, potential participants. The Trial Manager may work with the Chief Investigator, programming, and/or communications teams on this. Be aware that anything involving communication to potential participants will require ethical review. Consider the audience(s) you are trying to reach when deciding which social media platform(s) to use.

A trial website and/or social media accounts can disseminate news about the trial (for instance, recruitment milestones, new sites opening, attendance at conferences, or results when these are publicly available).

6.4 Data protection - the practicalities

Day-to-day management

Only collect data that is fit for purpose, approved by an ethics committee and in accordance with GDPR requirements. The sponsor and your institution's information governance team will have specific guidance on data management and may require production of a Data Protection Impact Assessment (DPIA) and/or Data Management Plan.

- Ensure adequate security and restricted access to both paper and electronic records.
- Ensure appropriate consent is obtained before collecting any participant data.
- 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.
- Ensure that you follow all data management procedures outlined in the trial IRAS application / DPIA / Data Management Plan
- Ensure that you are collecting the minimum amount of data necessary; it is inappropriate to collect data "in case it is useful later"

Key points - paper

- Document where paper files will be stored.
- Store securely 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.

Key points - electronic

- Restrict access to systems via password and user access management.
- Password-protect email systems.
- Use a secure network, i.e. one that is maintained by your host institution/Sponsor with appropriate IT support.
- Use a daily back-up — stored off-site.
- Make sure an audit trail is maintained.
- Never transfer study data to a personal device
- Avoid personal identifiers in email correspondence.
- Use encryption and coded identifiers for personal data.
- Establish secure methods of data collection and transfer and stick to these; ensure that sites do too.
- Know your institution's IT and data protection policies.

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

6.5 Monitoring

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

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

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

Monitoring while the trial is ongoing should include the following:

- Confirmation of participant consent — check that signed consent forms have been fully and correctly completed, either during site-monitoring visit or when received centrally.
- Confirming that sites are reviewing and complying with eligibility criteria before randomisation of participants.
- Review of primary outcome data.
- Data 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, with this clarification and correction being appropriately documented.
- Review of IMP management, including completion of all relevant forms and logs; if an ATIMP trial, monitoring compliance with traceability requirements.
- Adherence to trial arms and treatment regimes.

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 (45).

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. All monitoring must be documented.

6.6 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 host 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 has implemented a fully risk-based inspection process and 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.

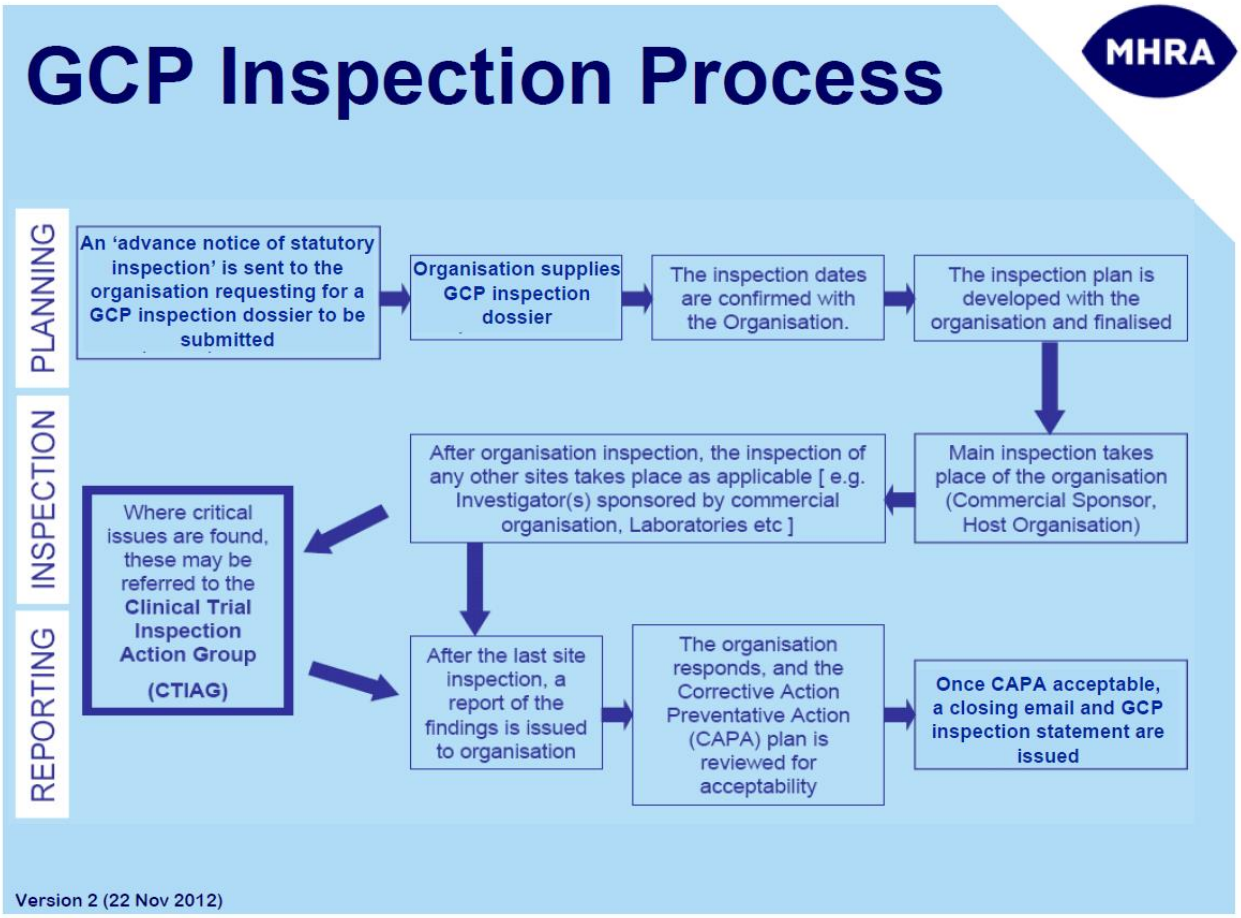
Notification of a routine inspection

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, and 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 in Figure 2 below:

Figure 2 GCP Inspection Process. Kindly reproduced from MHRA 2012.



What preparation is required for a routine inspection?

Alongside the preparation and submission of the dossier, you may be expected to work with the Quality Assurance Team to support other key preparatory activities, such as:

- Appointing an inspection coordinator to act as the lead contact responsible for all communication with the MHRA relating to the inspection.
- Reviewing previous and common findings and identifying areas of risk.
- Establishing a work plan, prioritising important issues.
- Developing 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

Reviewing essential documentation

During the inspection, essential documentation will be reviewed. 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.

- Ensuring necessary access to electronic systems such as databases if electronic data capture is performed; alternatively, 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.
- Confirming that all regulatory, ethical and local approvals, were obtained prior to the trial start.
- Reviewing 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.
- Ensuring 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.
- Confirming the whereabouts of the documentation and data for any archived trials and ensuring that written information from the archive site is available and that the data are stored in accordance with data protection legislation.
- Auditing or monitoring premises, services and trials that may be selected for inspection.
- Developing corrective and preventative action plans for any potential deficiencies identified, including a timeline for implementation.
- Ensuring that notes to file / file notes are up-to-date. These may be reviewed by the MHRA during the inspection.
- Considering the need for any further system development and preparing 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 (CTU/Sponsor) 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 six 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 http://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials.

6.7 Drug management systems

The manufacture, packaging, labelling, distribution, prescription, secure storage and accountability of 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 must be in place prior to the start of the trial.

- 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. Distribution methods need to be reliable, economical and budgeted for.
- Effective drug management is particularly important in an international multisite trial. For international multi-centre trials, 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 and any expired drugs, during and at the close of the trial, will need to be developed early in the planning stage.
- All trial drug packs distributed will need to be accounted for at the close of the trial.

Trial medications may be supplied from one or more central locations and distributed to local pharmacies, who would then be responsible for ensuring that the correct medication per allocated trial arm is given. It is the Trial Manager's responsibility to ensure that local pharmacy staff are trained on the protocol and key procedures. You may also need to implement systems or SOPs and oversee communication relating to medication distribution and allocation. 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 to misallocation of intended trial medication.

Remember: if the trial involves a drug and the Coordinating Centre is providing specialised labelling for the trial intervention, this must be compliant with Annex 13 (46). ALWAYS consult a Trial Pharmacist in the first instance.

For ATIMP trials, be aware that the Principal Investigator should:

a) Have 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 of 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.

In these trials, the product may be patient-specific and may be shipped directly to the investigator site or the participant rather than via pharmacy. In that case, pharmacy should be made aware of this 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 the arrangements.

Unblinding/unmasking

If the trial is blinded, 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 that 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 unblinding. If there are concerns about side effects but there is no clinical need for knowledge of the trial intervention for future management, the intervention can be stopped or interrupted temporarily or permanently without unblinding.
- If reporting potential Suspected Unexpected Serious Adverse Reactions (SUSARs) to regulators or pharma collaborators.
- 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. a 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, seven 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 refer-on process. Ultimately, the Chief Investigator is responsible for ensuring the trial blinding and that integrity is maintained. However, the ability to unblind participants directly must also be provided to sites 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.

6.8 Safety management and reporting systems

ICH-GCP states 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 (5) 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 https://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 regard 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 2004/1031 (8). Additional safety reporting considerations should also be considered for ATIMP trials as laid out in Regulation (EC) No 1394/2007 (21) and in the Human Tissue (Quality and Safety for Human Application) Regulations (SI 2007/1523) (28). Clinical Investigations and trials of a CE-Marked Medical Device used for their intended purpose use the definitions based upon ISO/FDIS 14155 (30). For other research, definitions relating to safety reporting are provided by the HRA. Check 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 very important that staff in the Coordinating Centre and participating sites are familiar with reporting requirements and procedures, including definitions, timelines and responsibilities, and that these are clearly documented. 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.

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 in the investigator brochure (IB) or summary of product characteristics (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 RSI may be detailed in the protocol or in a supplementary document e.g. in an expected adverse events list. The RSI must be reviewed annually and this review must be documented.

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 could continue 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 if they can cause the participant not to be allocated to randomised treatment (for instance, 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 Medicines for Human Use (Clinical Trials) Regulations 2004 (8) state, “An investigator shall report any serious adverse event which occurs in a subject at a trial site at which he is responsible for the conduct of a clinical trial immediately to the sponsor.” 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 people are the eligible target population for the trial.
- Whether it is necessary to follow up pregnant partners of a trial participant.
- How to obtain consent to follow up a pregnancy in a trial participant or their partner.
- How long after completion of study treatment by the trial participant or their partner 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) what precautionary actions may be required.
- Guidance about advice/counselling that should be provided to the pregnant participant/ their pregnant partner.
- Whether special obstetric care arrangements are necessary and how these will be monitored.
- Whether follow-up of the new-born for a period post-delivery is appropriate and, if so, for how long.

Urgent safety measures

An urgent safety measure is a procedure not necessarily defined by the protocol that can be put in place with immediate effect without needing to gain prior 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 (and the DMEC), 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), you may need to apply to the Funder/Sponsor for an extension. This can be a funded or a non-funded extension. Such applications should be made well in advance of your planned end date and be approved by the TSC prior to submission. The Funder will need to see good, clear, justifiable reasons for any extension. If the trial is funded as part of a wider programme (such as NIHR Programme Grants for Applied Research [PGfAR]) it may be possible to extend recruitment within the existing grant without requesting an extension from the Funder. Consideration should be given, however, to knock-on effects of this to other timelines within the grant.

If the end of trial date is extended, all relevant approvals for this change should be obtained. 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 data analysis and the database lock. Please ensure that your collaborative team have all seen this. Any change to the end of study definition after approval has been given for the research, should be notified as an amendment to the appropriate review bodies.

7.3 End of the recruitment period

Trial recruitment will close either as per protocol or prematurely. If the latter, it should be upon the recommendation from the DMC endorsed by the TSC or by the trial TSC, in the absence of a DMC. Trial recruitment may end prematurely also as a result of the withdrawal of funding. Ensure that the randomisation or recruitment system is disabled at the end of recruitment and that all collaborators are fully aware of this. It may also be appropriate to inform current participants if recruitment has ended prematurely.

7.4 Early termination or temporary suspension of the trial

A trial can be terminated early if the DMC and TSC (or TSC only in the absence of DMC) agree that there are safety concerns, it is unethical to recruit further participants, e.g. the treatment effect is definite with a smaller population or if funding or consumables are withdrawn or no longer available.

If the trial is terminated early or is temporarily suspended, the Sponsor should be notified immediately. The REC and the MHRA should be notified by completing the End of Trial Form and submitting this via IRAS within 15 days of closure For CTIMPs that were not submitted through combined review, the form should be emailed to the MHRA and REC.

Notify HRA of the end of trial for studies with HRA and HCRW approval only (no REC approval) and NHS R&D offices in accordance with local policies/procedures.

All investigators must be informed using expedited means of communication. The reasons for early termination or temporary suspension should be explicit and any follow up measures outlined. Consideration should also be given as to what and how information should be given to the trial participants. Funders should also be notified.

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. Obligations should be set out and communicated clearly at appropriate time points.

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

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

Informing participants

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

Informing the Sponsor

Making the sponsor aware that the trial has ended is a priority. The Trial Manager should ensure that the Sponsor is 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. An End of Study Declaration Form should be sent 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.

7.6 Site close-out

Once the trial is completed at site, check that the site file contains all essential documentation reflecting the end of the study, including a copy of the End of Study Declaration Form. Confirm the archiving arrangements (see Section 9). Close-out can either be done remotely or by conducting a site visit.

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

7.7 For CTIMP trials: trial drug supplies

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

7.8 Financial closure

When the trial closes to recruitment, the Trial Manager will have a role in ensuring that all recruitment payments to sites have been made. Reimbursement may also be made after the follow-up period on return of clean and complete CRF data. In addition, the Trial Manager should check that any payments due to third party suppliers (e.g. couriers, IMP supplier) have been made. It can be helpful to meet with your local budget holder/finance officer to help reconcile the budget, if required by the Funder.

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 an initial draft. 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 that began before 2021, 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 guidelines (47) 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.

A summary of results should also be sent to the Research Ethics Committee within the same timeframe.

For CTIMPS that began after 1st Jan 2021 and went through the Combined Review process, submission of results to EudraCT are not required. Instead, the end of the trial declaration is completed and submitted to the MHRA through IRAS. More information can be found on the HRA website: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/step-step-guide-using-iras-combined-ways-working-cwow/#reporting

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 https://www.health.org.uk/publications/section-2-communicating-your-research-results.

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, see https://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 https://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. This is done via the final report form on IRAS.

Where research has been reviewed by REC only submit the final report via HRA website.

8.3 Reporting to participants

Participants should be informed of the trial results. This could 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. The intended plans for dissemination of results should be detailed within the initial IRAS application.

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 up front. Check if the Sponsor/Funder or host organisation has any additional requirements to deposit publications in a specific repository. It is helpful to keep a record of all research outputs during the lifetime of the trial.

Section 9 Archiving

The documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced are defined as essential documents according to ICH-GCP, see https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.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 and/or contractors such as pharmacies, 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 for 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 - archiving requirements for CTIMPs can be found at www.legislation.gov.uk/uksi/2006/1928/regulation/18/made.

When preparing to archive trial records and documents there are several important considerations to factor into the process, 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 records, archiving may be the responsibility of IT staff. The archivist is responsible for:

- checking the facilities to be used are appropriate
- controlling and keeping a record of access to the archive (e.g. in the form of a log)
- maintaining a recording of what is held in the archive
- 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, for purposes of traceability.

9.2 Multisite trials: site documentation

The Principal Investigators are responsible for archiving essential documents at their respective sites in accordance with the Sponsor's requirements and any local requirements at the site or host institution. A Sponsor may arrange for a third party to archive site files on behalf of a site/host institution however this does not change who may access the records. Access to the archive 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 may 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 during the period of archival, may no longer be available or becomes obsolete. Appropriate backup of electronic data must be considered to mitigate against potential storage media failure. A review schedule to read and test records based on the risk of media failure should be set up and implemented. Access to data must be limited and managed and integrity controls in place to ensure that records cannot be altered and only 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.

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 the 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's 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://www.ukri.org/wp-content/uploads/2021/08/MRC-0208212-MRC-policy-and-guidance-on-sharing-of-research-data-from-population-and-patient-studies-Word-version-v01.02.pdf.

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