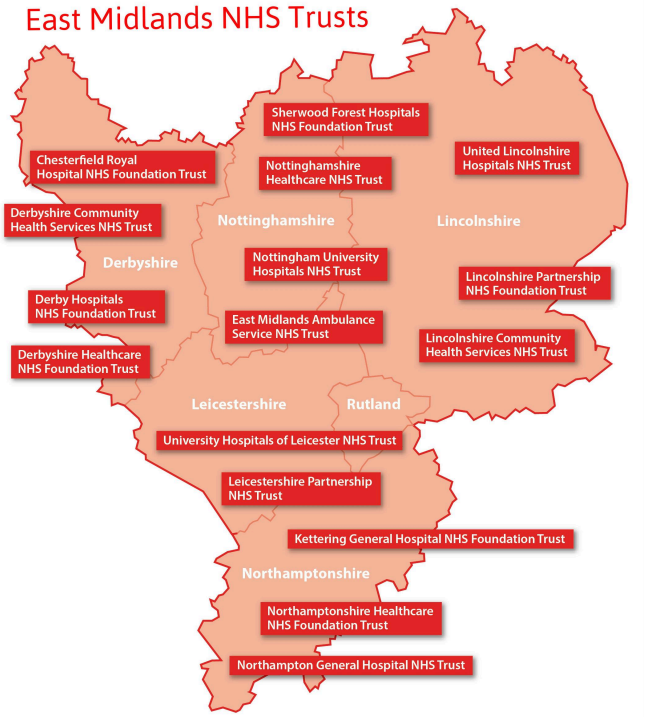
Clinical Research Network
East Midlands

National Institute for Health Research



NIHR Clinical Research Network East Midlands Induction manual for Research Staff

Acknowledgements: Clinical Research Network: South London Workforce Steering Group

Introduction

The purpose of this manual is to help orient you to your new role working for the Clinical Research Network East Midlands or at one of it's partner organisations. It sets out the key areas of knowledge required and is focused on helping you during your initial period in post (first 3 months).

This manual should be used in conjunction with the CRN East Midlands online induction which provides an introduction to the organisation.

This manual contains a summary of key topics and subtopics, followed by a list of other resources should you wish to extend your knowledge further in a specific area. There are specific links which you can click to access a range of documents and resources.

Research Work Topics

1A Study Design

Understanding Clinical Research

Research methodology is complex and only a very brief outline of the most relevant information will be presented here. There are a number of different research methods which use differing rules and are underpinned by different philosophies. Each have their strengths and weaknesses and when research needs to be carried out, the type or combination of methods chosen will depend on the type of research question to be answered, as well as the skills, knowledge and preferences of the researchers.

Clinical Trials

A clinical trial is a research study in volunteers which is designed to answer specific health related questions, for example, to find out the best way to treat, screen, diagnose and/or prevent disease. Data collected during the study can provide information on whether a new treatment or procedure is safe, what (if any) the side effects are, and whether it is better than the current standard treatment.

Clinical trials are usually conducted in phases. These range from Phase I to IV. The trials at each phase have a different purpose and help scientists answer different questions. Given below is a brief description of what these phases entail.

Phase I

These trials are initial clinical tests of new potential treatments in which researchers test an experimental drug or treatment in a small group of participants (up to 30 participants, but often a lot less). Phase I trials determine the safe dose range, the effect of the drug on the body (i.e. common side effects) and the way the body affects the drug (pharmacokinetics). These trials often use healthy volunteers but they may also include patients with the disease in a stable state or with advanced stage disease (e.g. patients with advanced cancer) who have exhausted all other treatment options. As with all trials they will be closely monitored and any side effects noted.

Phase II

These trials involve a larger number of participants who have the disease for which the treatment is being assessed. They are designed to test the efficacy of the new treatment (i.e. if it is effective in the indicated disease). Information on side effects and tolerability is collected in this phase so that some less common side effects and cumulative effects might become apparent.

All phase I and non-randomised phase II trials fall under the heading of translational research. This is a term used to define experimental research of new treatments and diagnostic procedures for all diseases. It covers all experimentation to develop new treatments, rather than comparing them against a standard treatment. Treatments only move into a phase III clinical trial if phase II is successful. Many trials do not proceed to the next phase.

Phase III

These trials are large national or international trials involving hundreds or thousands of participants. They are comparative studies designed to compare the effects of new drugs or treatment methods. These studies can investigate the new treatment to replace standard therapy or as an addition to standard therapy. Participants are usually divided at random into either the treatment intervention group, or a control group. Participants in both groups are usually as similar as possible.

Further and more reliable information can be gathered about efficacy in this stage i.e. how well the treatment works and how long the benefits last on average. Safety monitoring ensures that less common side effects and possibly any longer term problems will also be revealed at this stage. Statisticians estimate how many research participants will be required to prove, with an acceptable degree of confidence (usually described as 95% confidence interval) that the results are not due to chance alone. Generally, if the expected improvements from the trial treatment are large, the differences will be measurable after a relatively smaller number of participants have been treated. If only a small improvement is expected, a larger number will need to be treated before the measured effect can be classed as significant (meaning the change is not due to chance alone). A Phase III trial should provide enough information for a new treatment or procedure to be used as the new ‘standard treatment’.

Phase IV

These trials are post-marketing studies, carried out after a treatment has been shown to be effective and has been granted a license from a competent authority (i.e. the Medicines and Healthcare Products Regulatory Authority (MHRA) in the UK or the Food and Drug Administration (FDA) in the US). Further information is gained about the effects of wider participation, longer-term risks and benefits, and more about possible rare side effects so that optimal use can be decided. These trials compare drugs that have become available for doctors to prescribe, not new drugs that are still being developed.

Outcome measures in clinical trials

An outcome measure is the means by which we determine the impact of an intervention on participants. Outcome measures are also known as response variables, events or endpoints. The outcome measure(s) selected for a trial will depend on the phase of trial, stage of disease and the intervention being tested. Early phase trials (phases I and II) commonly use outcome measures of disease response whilst late phase trials (phases III and IV) use outcome measures that include survival (disease free or overall survival). Almost all clinical trials will include some measure of safety and treatment compliance.

Other Research Methods and Types of Studies

Epidemiology

This is the study of factors that might affect the health and illness of populations. It is used in public health research, identifying risk factors for disease and can sometimes demonstrate optimal treatment approaches to maintain public health.

Observational studies

These include individual case studies, case control studies, and cohort studies (using a particular group of participants e.g. participants with a strong family history of cancer). There is no active intervention in these studies. Investigators observe their participants and measure outcomes. They are looking for correlations (associations) between different factors e.g. various risk factors such as lifestyle, diet, environment, family history and genetic predisposition, and health status or outcomes of disease and treatment.

Quantitative Research

Quantitative research methods are based on measuring and counting observed phenomena (objective data) and use mathematical models and statistics, usually with large numbers of participants. Most clinical trials use quantitative research methods of data collection and analysis.

Qualitative Research

Qualitative research is usually based on a more in depth study of the subject matter, using a smaller number of participants. It involves subjective description rather than objective measurement and allows the social/environmental context and the investigator to be central to the research process rather than being removed from it. Although clinical trials are considered to be the ‘gold standard’ method when trying to measure the effects of a discrete medical intervention, qualitative methods might be better when a deeper understanding of the impact is required, for example when trying to understand human behaviour or complex social phenomena. Qualitative methods can be used to evaluate the effects of more complex health or social interventions. Some health and social care studies will use a mixed methods approach.

Systematic Reviews

A systematic review is classed as secondary research. This is the analysis of published or recorded data from previously conducted research projects. Systematic and explicit criteria are adopted to identify, select and critically appraise research studies to establish where the effects and effectiveness of healthcare interventions are consistent and where they vary.

Meta-analyses

Meta-analyses occur when statistical methods are applied to the review and analysis of combined data from studies included in a systematic review. This enables the power of any observations to be increased so that small non-significant studies can be combined with each other to determine whether a true effect is present or not.

1B Research in the NHS

All health and social care research carried out in the UK is governed by strict regulations. They exist to ensure that research is carried out consistently to high ethical and scientific standards, and to prevent poor

performance, adverse events where possible, research misconduct and fraud. They also help to ensure that lessons are learned and shared when poor practice is identified. Organisations involved in clinical research have a duty to foster a high quality research culture and individuals have a duty to ensure that they, and those they manage, are appropriately qualified by training, education and experience for the roles that they undertake.

UK Policy Framework for Health and Social Care Research

This policy framework sets out principles of good practice in the management and conduct of health and social care research in the UK. Find out more here.

1C Other Guidance & Legislation

The Declaration of Helsinki 1964

The Declaration of Helsinki is the original key document that protects the rights of individual participants in the field of bio-medical research throughout the world. It was produced in 1964, and has been revised on a number of occasions; a copy of the most up to date version can be found here.

The European Union Directive of 2001 (2001/20/EC)

The European Union (EU) Clinical Trials Directive (2001/20/EC) aims to harmonise and streamline clinical trials procedures throughout the member states, and relates to interventional studies, i.e. Clinical Trials of Investigational Medicinal Products (CTIMPs). It encompasses all personnel involved with the clinical trial procedures and applies to all sites undertaking interventional research. It was subject to an amendment in 2005 (directive 2005/28) which has also been subsequently incorporated into UK law.

Medicines for Human Use (Clinical Trials) Regulations 2004

This act (statutory instrument 2004/1031) transposed the EU directive into UK law. It enshrines International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines in UK Law (see below) and compels all parties practicing research to adhere to them. It has been amended several times to incorporate clauses for emergency research, research involving vulnerable groups (adults lacking capacity and children) and most recently research in pandemic situations.

Good Clinical Practice (GCP)

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involved the participation of people. GCP is applicable to all clinical research.

Until 1997, there were several documents relating to good clinical practice (GCP). An international committee for the harmonisation of good clinical practice (ICH GCP) was formed to produce a standard agreed by the European Union, Japan and the United States. These guidelines were implemented in the participating countries, and had the advantage of facilitating mutual acceptance of data by the regulatory authorities of those countries.

The ICH GCP guidelines are very comprehensive and list responsibilities for all involved in research activity. It includes specific sections listing responsibilities of ethics committees, investigators and sponsors. There are also sections detailing the format of trial protocols, investigator brochures and essential documents required for clinical trials.

Since the finalisation of the ICH Good Clinical Practice (GCP) Guideline in 1996, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. This guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. ICH GCP E6 (R2) addendum can be found here.

Medicines and Healthcare products Regulatory Agency

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe. The MHRA is the 'competent authority' in the UK which regulates clinical trials of investigational medicinal products (CTIMP's) and ensures that they comply with the law.

Their aims are to:

- Protect public health through regulation, with acceptable risk: benefit profiles for medicines and devices.
- Promote public health by helping people who use these products to understand their risks and benefits.
- Improve public health by encouraging and facilitating developments in products that will benefit people.

Data Protection Act 1998

The Data Protection Act (DPA) was introduced in response to the European Community Data Protection Directive 1995. It applies to personal information, which must be processed in accordance with eight main principles. Data should be:

- Fairly and lawfully processed
- Processed for limited purposes
- Sufficient and relevant
- Accurate
- Not stored for longer than is necessary
- Processed in line with data subjects' rights
- Secure
- Transferred only to countries with adequate security

The nature of research means that there is a large amount of paper and electronic data held about research subjects. Research staff have a responsibility to their research subjects and their employer regarding data protection:

- All subject data should be stored in a secure room
- All subject data must be locked away if unattended
- No one should access subject data unless authorised to do so by research personnel and/or a data protection officer. Subject confidentiality should be maintained by use of initials/numbers on research material where appropriate
- Electronic data must be password protected in accordance with the IT Security Policy
- Personal data that has the potential to identify research subjects should be kept in a secure place
- All staff should be familiar with their institutions' data protection policies. All members of staff dealing with data, which is regarded as being sensitive, must sign a data protection statement to say that they have read and understand this document. This statement also requires staff not to discuss

confidential data unless required as part of their job. Any concerns relating to data protection issues must be discussed with your line manager.

The Human Tissue Act 2004

This was introduced to regulate the removal, storage and use of Human Organs and Tissue.

The act:

- Streamlines and updates current law on organs and tissue so that current gaps and anomalies are put right and the system is made fit for the 21st century.
- Provides safeguards and penalties to prevent a recurrence of the distress caused by retention of tissue and organs without proper consent. Tissue or organs cannot be taken or kept without consent other than for a Coroner to establish the cause of death.
- Sets up an overarching authority which will rationalise existing regulation and will introduce regulation of post mortems and the retention of tissue for purposes like education and research.
- Provides for the Human Tissue Authority to issue Codes of practice giving practical guidance on the conduct of activities within its remit.
- Will help improve public confidence so that people will be more willing to agree to valuable uses of tissue and organs like research and transplantation.
- Will improve professional confidence so that properly authorised supplies of tissue for research, education and transplantation can be maintained or improved.

Ionising Radiation (Medical Exposure) Regulations

Ionising Radiation Medical Exposure Regulations (IRMER) trials involving any radiological investigations (e.g. chest X-ray; CT scan; radiotherapy) must be reviewed by a radiologist in order that the following legislation is considered.

The Ionising Radiation (Medical Exposure) Regulations (2000)

Trial patients are often exposed to higher levels of radiation than non-trial patients as they undergo more tests and imaging to monitor progress and response to trial treatments. This Act (amended in 2006) requires staff involved in undertaking medical exposures to establish Diagnostic Reference Levels (DRLs) and to undertake appropriate reviews if these are consistently exceeded.

The Department of Health and Social Care has issued guidance on national DRLs, for more information see here.

ARSAC: Administration of Radioactive Substances Advisory Committee

Administration of Radioactive Substances Advisory Committee (ARSAC) trial patients are often exposed to higher levels of radiation exposure than is necessary for routine diagnosis and treatment. This is allowed but an ARSAC research certificate must first be obtained for each research project which exposes patients to these higher levels. ARSAC assesses each application on its own merits and while it is important to keep doses as low as reasonably practicable, the activity administered (and the resulting dose) should be that necessary to provide the information required. All ARSAC certificates are site-specific, therefore in the case of multi-centred studies, each study site requires its own certificate.

Topic 2: Study Set-up

Before any study can be run in an NHS setting there are certain approvals that must be obtained to confirm appropriate checks have been conducted and relevant permissions are in place.

2A Study Feasibility and Site Set-up

It is important that work is undertaken at the earliest stage to establish feasibility for any proposed study in an NHS setting. Each study has protocol requirements and funding support which will impact how feasible a particular study is for a specific NHS site, with its own particular set of resources and patient populations and care pathways. Each NHS site may have its own formal approach to conducting feasibility and it is important to be aware of this when assisting in study set up. Key departments in this process will be the organisation's Local Research & Development/Research & Innovation Department and the Study Support Service of the CRN East Midlands together with the organisation's relevant clinical departments and R&D/R&I mechanisms for study set up.

2B NHS Permissions Process

Before you are able to start recruiting participants into a study you must have received the appropriate regulatory approvals to do so. All research carried out within NHS organisations requires prior agreement to proceed. Guidance on the approvals required can be found on the Health Research Authority (HRA) website

https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/

In addition, Clinical Trials of Investigational Medicinal Products (CTIMPs) require approval by the MHRA and a European Union Clinical Trials Database (EudraCT) number.

National Research Ethics Service Research Ethics Committee (NRES REC) Approval

All NHS RECs (formerly known as NRES RECs) are established by the Health Research Authority for the purpose of reviewing applications within the Governance Arrangement for Research Ethics Committees (GAfREC).

The primary function of a REC when considering a proposed study is to protect the rights, safety, dignity and well-being of all actual or potential participants, in the NHS. The REC is entirely independent of the researcher and the organisations funding and hosting the research.

Any health-related research project which involves NHS patients, their tissue and/or data must be reviewed by a NHS REC prior to it commencing.

RECs review applications for research and give an opinion about the proposed participant involvement and whether the research is ethical.

Topic 3 Study Conduct

3A Key Personnel
Some of the key roles and responsibilities within a study are outlined below.

Chief Investigator (CI)

- Responsible for the design, management and reporting of the study for all sites
- Responsible for ensuring that each investigator is aware of their legal duties and obligations
- Responsible for ensuring the protocol is approved by relevant bodies, any pre-conditions are acted upon, and that research follows the agreed protocol except in the case of urgent safety measures
- Undertakes duties delegated by the sponsor (usually working in conjunction with a Clinical Research Organisation (CRO) if it is a pharmaceutically funded trial)
- Publishes the clinical study results as soon as possible following study completion. In a multi-centre study, the CI must ensure that the data from one centre is not published before the publication of the whole study without his/her consent, and must obtain sponsor approval prior to publication.

Principal Investigator (PI)
The PI is responsible for the conduct of the study at a particular site. It is the responsibility of the PI to conduct the study according to the protocol and to ensure that he/she has the necessary patient population available to conduct the study within the period defined in the study protocol.

Research Nurse, Allied Health Professional, Research Practitioner and other members of the research delivery team
The Research Nurse, Allied Health Professional (AHP) and Research Practitioner have their responsibilities delegated by the PI, these responsibilities may include:

- Preparing & submitting local regulatory approval applications
- Ensuring that they have attended an initiation meeting and received any appropriate training prior to the trial commencement
- Co-ordinating the clinical trial in terms of patient screening, recruitment, entry into the trial via randomisation if applicable and subsequent patient visits
- Checking patient eligibility according to the inclusion/exclusion criteria stated in the protocol in collaboration with medical staff
- Collaborating with clinicians in assessing patients and making treatment decisions according to the protocol
- Delivery of investigational agents/treatments and protocol directed care
- Handling, spinning, labelling, storage and shipping of blood and urine pharmacokinetic samples
- Ensuring that source documentation is a true reflection of decisions and actions taken for each individual patient
- Completion of case report forms and ensuring relevant follow up data is collected (e.g. quality of life data). Under current funding regulations CRN research support staff will largely be involved in study screening and recruitment, only and involved in follow up aspects of studies in so far as required by safety requirements of GCP.
- Monitoring and reporting all safety events: SAEs, SARs, SUSARs etc, as outlined in the protocol, including prompt reporting to the study sponsor to ensure further action to MHRA/REC within statutory timelines.
- Liaising with the study sponsor regarding the conduct of the trial
- Educating patients/subjects and dissemination of trial related information to staff.

3B Consent

It is morally and professionally unacceptable to perform any research related procedure on someone without receiving their fully informed consent. The issue of informed consent has prompted great discussion and thought, and is a key issue in clinical research.

Gaining informed consent in research which involves invasive procedures is a legal requirement. As in all other aspects of clinical trial legislation, the Medicines for Human Use (Clinical Trials Regulations 2004) details the statutory requirements for informed consent of participants in Clinical Trials of Investigational Medicinal Products (CTIMP) whilst the UK Policy Framework for Health and Care Research provides guidance for non-CTIMP studies; however, a number of other UK laws are also relevant to the consent process.

If a research activity proceeds without an individual's informed consent legal action could be taken against the CI or researcher. Case law on consent in the UK has established three requirement to be satisfied before a potential research participant can give informed consent:

- The consent should be given by someone with the mental ability to do so
- Sufficient information should be given to and understood by the participant

- The consent must be freely given.

When?
Informed consent should be received from patients prior to any research related procedure being performed.

How?
- An ethics committee approved information sheet and consent form must be used
- Informed consent form must be up to date and revised if new information becomes available (must be re-approved by ethics committee if changed)
- All information sheets and consent forms should also meet local site approval.
- No coercion of subjects to participate
- Language of informed consent should be understandable and not cause subject to waive or appear to waive or release investigator, institution or sponsor from responsibilities
- Inform subjects of important information, including risks and side effects
- Language should be as non-technical as possible
- Allow subject time to review information before signing
- Allow time to answer questions and review issues raised by subject
- Consent form to be signed and dated by subject or legally responsible person e.g. parent and person obtaining consent
- Subject must keep a signed copy of the consent
- Subject's legal rights must be maintained at all times.

Consent is an ongoing state
It is essential to remember that even once a patient has signed an informed consent, they can withdraw from the study at any time, without giving a reason. It is the duty of the investigator to reiterate this and reassure them that they will not compromise their future medical care if they decide to withdraw.

Who?
Overall responsibility for all elements of research activity, including gaining informed consent, rests with the PI. Although others may play a major role in the consent process (explaining procedures, answering questions, etc), for studies involving medical intervention, the ultimate responsibility for enrolling the subject lies with the investigator who is usually a medically qualified Doctor or Dentist (in non intervention studies the investigator may not necessarily be medically qualified). The PI may delegate the task of obtaining informed consent to another appropriately qualified and experienced member of the research team, but this delegation must be clearly documented, and the person gaining informed consent must sign and date the consent form.

The investigator should ensure that subjects have fully understood what they are consenting to and sign and date the consent form accordingly. Any other research personnel involved in giving information during the informed consent procedure should also sign the informed consent form.

This approach meets the criteria of the key documents, and adheres to the Declaration of Helsinki.

Further requirements for consent
For research involving minors and incapacitated adults, the EU directive (2001/20/EC) states that such persons may not be included in clinical trials if the same results can be obtained using people capable of giving consent. Where research is deemed to be necessary to improve outcomes specifically for these

vulnerable groups, strict rules apply. These are summarised below.

Mental Capacity
Mental capacity is the ability to make a decision. Lack of capacity can be temporary or permanent and may be due to a range of causes, including unconsciousness, dementia, learning disabilities, stroke, head injuries, mental health problems, and possibly cancer metastases in the brain. Capacity can only be assessed in relation to a particular decision and a particular time. A person may have the capacity to make some decisions but not others, or their capacity may vary over time.

Research Involving Minors (defined as < 16 years of age)

- Informed consent of parents (or legal representative): a parent or person with parental responsibility should always be approached if available; if not a personal/professional legal representative not connected with the conduct of the trial may be approached.
- Must represent presumed will and can be withdrawn
- Minor must receive information according to his/her understanding
- Information must be given by staff with experience
- No incentives or financial inducements
- Direct benefit for that specific group of children
- Ethics approval from a committee with paediatric experience
- EU Directive: Article 4 (Directive 2001/20/EC).

Research Involving Adults Lacking Capacity

- Consent of the legal representative
- Must respect the subject's presumed will and can be withdrawn at any time
- Subjects must receive information according to their level of understanding
- No incentives or financial inducements
- Direct benefit for that specific group of patients
- Ethics committee with expert in the relevant area must approved the protocol
- EU directive: Article 5 (Directive 2001/20/EC)
- Mental Capacity Act (2005) provides parameters for non-CTIMP studies

Reference Resources
ICH Harmonised Tripartite Guideline for Good Clinical Practice ICH GCP 1996, Section 4.8

NHS Research Ethics Service http://www.hra.nhs.uk/

The Mental Capacity Act (2005) - Adults with Incapacity (Scotland) Act (2000)
http://www.legislation.gov.uk/ukpga/2005/9/contents

The Medicines for Human Use (Clinical Trials) Regulations (2004)
http://www.legislation.gov.uk/uksi/2004/1031/contents/made

Royal College of Paediatrics and Child Health (2000) Guidelines for the Ethical Conduct of Medical Research involving Children
http://adc.bmj.com/content/82/2/177.full.pdf

Medical Research Council (2004) MRC Ethics Guide – Medical research involving children, MRC; London

The Children's Act (2004) http://www.legislation.gov.uk/ukpga/2004/31/contents

Royal College of Nursing Research Society (2011) Informed consent in health and social care research RCN guidance for nurses 2nd edition, RCN; London

3C. Protocol, Specific Requirements & Standard Operating Procedures

A protocol is the document that describes the objective(s), design, methodology, statistical considerations, conduct and organisation of a trial. It is in effect an 'instruction manual' for research teams to ensure that they all adhere to the same methods and procedures when conducting the trial. A protocol amendment is a written description of a change(s) to, or formal clarification of a protocol. A protocol and any amendments to it must have received appropriate approvals before it can be implemented.

When reading a protocol, you should identify the main sections and consider against the context of your role & responsibilities in the study.

Standard Operating Procedures (SOPs) are defined in the ICH-GCP guidelines as "detailed written instructions to achieve uniformity of the performance of a specific function." The aims of SOPs are to ensure that any procedure performed as part of a research trial is done to a consistently high standard, thus enhancing the quality of the data produced. SOPs are of particular importance when a trial is being run over several sites, and involves a number of research personnel.

SOPs are relevant to all aspects of a research trial. That is, general study organisation, pre-study procedures, actual studies procedures and end of study procedures. As a general rule, anything that is done as part of a research trial should have a SOP. Before commencing a trial specific procedure, the appropriate SOP should be read.

SOPs should be written by those performing the procedures, to ensure that they are a workable record of what actually happens. To achieve their purpose, SOPs need to be easy to read and implement. Once they are written, SOPs should be reviewed and updated regularly to ensure that they are up to date and relevant to practice.

Good practice would indicate that a central file of SOPs for research staff should be available to access as and when required. Research staff are likely to be actively involved in writing, reviewing and developing SOPs.

Each team, department or organisation will have a set of SOPs which give clear instructions on the processes involved in the day to day management of clinical trial procedures. These documents are extremely important to your daily practice and it is strongly recommended that you obtain copies and refer to them regularly, always ensure that you are reading the correct version of these documents.

The above is an outline to the procedures involved in running a trial in a clinical setting. Much of the information you will need is contained on the Clinical Trials Toolkit website: www.ct-toolkit.ac.uk. This is a one-stop online information resource for staff participating in UK publicly funded clinical trials, launched in

2004 by the Medical Research Council and Department of Health. You should also refer to your local clinical study SOPs as you work your way through the information in the website.

Topic 4 Data Quality and Management

4A Confidentiality and Data Protection

Principles of Data Protection
Anyone processing personal data must comply with the eight enforceable principles of good practice. The principles say that data must be:

- Fairly and lawfully processed
- Processed for limited purposes
- Adequate, relevant and not excessive
- Accurate
- Not kept longer than necessary
- Processed in accordance with the data subject's rights
- Secure
- Not transferred to countries without adequate protection

Clinical Research staff have a responsibility to their research participants and their employer regarding data protection:

- All participant data should be stored in a secure room
- All participant data must be locked away if unattended
- No one should access participant data unless authorised to do so by research personnel and/or data protection officer
- Personal data that has the potential to identify research participants should be kept in a secure place, separate from the research files
- Participant confidentiality should be maintained by use of initials/number on research
- material
- Electronic data must be password protected - in accordance with the IT Security Policy.

Any concerns relating to data protection issues must be discussed with the relevant data Protection officer. All staff should be familiar with the data protection policies of the organisation to which they are accountable under NHS governance regulation.

Medical notes must be stored in accordance with each NHS organisation's policy, e.g. the NHS Trust's policy.

Principles of General Data Protection Regulation

From the 25 May 2018, General Data Protection Regulation (GDPR) came into force. You will find some guidelines and useful resources issued by the HRA, MRC and the UK Government. The NIHR Privacy policy can be found here.

- Lawfulness, fairness and transparency
- Purpose limitation
- Data minimisation
- Accuracy
- Storage limitation
- Integrity and confidentiality (security)
- Accountability

Information Commissioner's Office (ICO) is the UK's independent authority you may access their website from here.

GDPR guidelines from our host, University Hospitals of Leicester NHS Trust can be found here. Guidelines from some of our partner organisations can be found on their websites:

Chesterfield Royal Hospital NHS Foundation Trust
Derbyshire Community Health Services NHS Trust
Derbyshire Healthcare NHS Foundation Trust
East Midlands Ambulance Service NHS Trust
Kettering General Hospital NHS Foundation Trust (pdf)
Leicestershire Partnership NHS Trust
Lincolnshire Community Health Services NHS Trust
Lincolnshire Partnership NHS Foundation Trust
Northampton General Hospital NHS Trust
Nottingham University Hospitals NHS Trust
Nottinghamshire Healthcare NHS Foundation Trust
Sherwood Forest Hospitals NHS Foundation Trust
United Lincolnshire Hospitals NHS Trust
University Hospitals of Derby and Burton NHS Foundation Trust
NHS Lincolnshire East CCG
NHS Corby CCG
NHS Derby and Derbyshire CCG
NHS East Leicestershire and Rutland CCG
NHS Leicester City CCG
NHS Mansfield and Ashfield CCG
NHS Newark and Sherwood CCG
NHS Nottingham City CCG
NHS Nottingham North and East CCG
NHS Nottingham West CCG
NHS Rushcliffe CCG
NHS South West Lincolnshire CCG
NHS South Lincolnshire CCG

4B Essential Documents

Essential documents are those documents which individually or collectively permit the evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator and their study team, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. Essential documents 'tell the story' of the study from beginning to end; most are stored in a trial master file or investigator site file.

An easy way to remember essential documents is to put them into two categories: Patient Specific and Trial (or non-patient) Specific.

Trial Specific /Patient specific

- Protocol including amendments Trial Specific
- Investigator brochure Trial Specific
- Sample patient information sheet & consent form
- Regulatory applications and responses / approvals
- Delegation log / CVs Trial Specific
- Study training records
- Correspondence / Newsletters
- Safety Reports
- Signed consent form: Patient Specific
- Case Report Forms (CRF) [data collection tool] : Patient Specific
- Data Queries
- Source documents – hospital notes / lab forms / reports etc. : Patient Specific

4C Data and CRF Completion

A Case Report Forms (CRFs) is a record of all the data and other information on each subject required by the research protocol. The ICH GCP guidelines include strict guidance relating to CRF completion, as they are the official documentation of the trial for the authorities. The CRFs, along with source documentation would be closely examined in the event of an audit.

The CRF should collect necessary information about:

- The patients
- Administration of the study drug
- Study specific procedures
- The outcome of any assessments
- Details of any adverse events.

Only those personnel identified by the PI should complete CRFs. These can include:

- The Principal Investigator
- Co-Investigators
- Research Nurses, Radiographers and Data Managers.

Anyone completing a CRF should have completed the signature log in the investigator/site file, and provided a copy of their CV. CRFs should be completed during, or as soon as possible after the associated visit/patient

assessment, to ensure that the information is up to date and accurate. Before any monitoring or audit visits, it is essential to ensure that CRFs are as up to date as possible.

Guidelines to CRF Completion

- Always use black ball point pen to complete a CRF
- Never leave blank spaces. If a section cannot be completed write, as appropriate: not known, not done etc
- All entries must be legible
- Corrections must be made as follows:
    - Cross out incorrect entry with a single line, so that the original entry is still legible.
    - Enter the correct data. Initial and date correction
    - If it is not obvious, then give an explanation for alteration
- Never enter a research subject's full name on a CRF
- The CRF for each patient must be signed off by the Principal Investigator to indicate that they believe that they are complete and correct.

CRF completion is one of the most important roles of the research staff, as it is the only source of data that will be received by the sponsor company. Therefore, accurate and thorough completion is essential.

4D Safety Reporting

Pharmacovigilance is defined as watchfulness in guarding against danger from drugs; it is the continuous process of monitoring, evaluating and improving the safety of medicines. In clinical trials there are defined procedures for reporting, monitoring and managing adverse reactions and events that satisfy the requirements of the law i.e. The Medicines for Human Use (Clinical Trials) Regulations. To comply with this Act organisations taking on Pharmacovigilance responsibilities need to make arrangements to record, notify, assess, report, analyse and manage adverse events in those trials.

The regulations distinguish between:
Adverse Events (AEs): Any untoward medical occurrence in a CTIMP subject (does not need to have a causal relationship with the IMP, but if there is, this is sometimes referred to as an Adverse Reaction).

Serious Adverse Events (SAEs): Any adverse event which results in death, is life-threatening, requires hospitalisation or prolongs hospitalisation, causes disability or incapacity, causes a congenital abnormality/birth defect, or other (specified by sponsor).

Serious Adverse Reactions (SARs): An SAE that has a causal relationship to the IMP.

Suspected Unexpected Serious Adverse Reactions (SUSARs): A SAR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator brochure or product characteristics).

It is the responsibility of the research team to notify the trials unit or study sponsor of SAEs, SARs and SUSARS within the time specified in the protocol. Systems must be in place to ensure that adverse events are assessed by the principal investigator or co-investigator for:

1. Causality (is it a reaction to a trial medicine or not?)
2. Expectedness (is the reaction a recognised adverse effect of the medication or is it unexpected?) The regulations allow the sponsor/CI to specify in the protocol SAEs that do not need to be notified immediately, for example if the event is one of the main expected outcomes in the trial (e.g. death). Sponsors have to make sure that SUSARS are reported promptly to both the regulatory authorities and the relevant Ethics Committee (within 7 or 15 days depending upon the outcome) therefore **prompt reporting by the site research team to the sponsor is essential.**

At the clinical level, there will be a local SOP for the reporting of SAEs which must be adhered to. In order to meet the tight reporting deadlines above, the clinical research team must report any SAE to the trials office as soon as possible and not later than 24 hours after first discovering that the event has occurred.

An annual safety report must be sent by the trials office to the regulatory authorities and relevant Ethics Committee. The report should include Adverse Events (AE) explicitly detailed in the protocol; all reported Serious Adverse Events, Serious Adverse Reactions and SUSARs.

4E Storage and Archiving

Essential documents must be retained (archived) for a sufficient period of time (according to the sponsor and R&D policies and procedures) to allow for audit and inspection by the regulatory authorities. They should be readily available upon request.

Storage

- Essential records should be maintained in a legible condition
- Archiving arrangements should be made at the protocol development stage of the research. Costs and storage should be considered
- Adequate and suitable space should be provided for the safe and secure storage of all essential records upon completion of the trial
- The archiving facility should be secure, with appropriate environmental controls and adequate protection from fire, flood and unauthorised access
- The documents can be stored by a sub-contractor (e.g. commercial archive) but the ultimate responsibility for the quality, integrity, confidentiality and retrievability of the documents resides with the sponsor (ICH-GCP).

Access to archives should be restricted to authorised personnel. An archive log or index should be maintained to record all essential documents that have been entered into the archive, and to track and retrieve documents on loan from the archive.

The sponsor should be made aware of the storage arrangements for the documents. If the investigator is no longer able to maintain custody of their essential documents the sponsor should be notified in writing and the investigator/institution must make appropriate arrangements.

Duration of Archive

The sponsor will need to consider whether the results may or may not be included in a marketing authorisation application and should take the appropriate steps to ensure appropriate retention of the essential documents. Consideration of site specific archiving requirements as detailed by each R&D Department, is essential as

these may differ from department to department.

Destruction of Essential Documents
The reason for destruction of essential documents should be documented and signed by a person with appropriate authority. This record should be retained for a further five years from the date that the essential documents were destroyed. The sponsor (or someone on the sponsor's behalf) should notify investigators in writing when the trial records can be destroyed.

Reference Resources:
The International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use. (1996) Guidelines for Good Clinical Practice (GCP) http://ichgcp.net/
Especially: ICH GCP, Section 8, Essential Documents for the conduct of a Clinical Trial EU Directive 95/46/EC (1995)

The Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

References Resources (Data Management):
Local resources:
Relevant Standard Operating Procedures (SOPs) - identified for you by your mentor
Each Research Protocol will contain information of the "data" to be collected and instructions on how to process it.

Key personnel:
Data Manager
Quality Assurance Manager
Clinical Trials Administrator/ Trials Coordinator
Feedback given by Trials Monitor
Patient Records Manager

Other Resources:
ICH-GCP guidelines

Information Commissioner's office online: gives brief and clear info on Data Protection
https://ico.org.uk/for-organisations/guide-to-data-protection/

Data Protection Act (1998)
http://www.legislation.gov.uk/

Information Governance and Caldicott Principles (last updated March 2012)
http://www.wales.nhs.uk/sites3/home.cfm?orgid=950
https://www.gov.uk/government/publications/the-information-governance-review

For staff working at a higher level of record management
Department of Health (2006) Records Management: NHS code of practice
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4131747

Medicines and Healthcare Products Regulatory Agency (MHRA)
http://www.mhra.gov.uk/index.htm

For research funding search, for example:
National Health Service website: www.nhs.uk
NIHR website: http://www.nihr.ac.uk/
Charitable Organisations such as MRC www.mrc.ac.uk
Wellcome Trust www.wellcome.ac.uk/

Patient and Public Involvement and Engagement

INVOLVE defines public involvement in research as research being carried out '**with**' or '**by**' members of the public rather than '**to**', '**about**' or '**for**' them. This includes, for example, working with research funders to prioritise research, offering advice as members of a project steering group, commenting on and developing research materials.

When using the term 'public' this refers to patients, potential patients, carers and people who use health and social care services as well as people from organisations that represent people who use services. Whilst all of us are actual, former or indeed potential users of health and social care services, there is an important distinction to be made between the perspectives of the public and the perspectives of people who have a professional role in health and social care services.

INVOLVE uses the following terms to distinguish between the different activities:

Involvement – where members of the public are actively involved in research projects and in research organisations.

Examples of public involvement are:

- as joint grant holders or co-applicants on a research project
- involvement in identifying research priorities
- commenting and developing patient information leaflets or other research material

Participation – where people take part in a research study.

Examples of participation are:

- participants being recruited to a clinical trial or other research study to take part in the research
- completing a questionnaire or participating in a focus group as part of a research study.

Engagement – where information and knowledge about research is provided and disseminated.

Examples of engagement are:

- open day at a research centre where members of the public are invited to find out about research
- raising awareness of research through media such as television programmes, newspapers and social media
- For further information please see the web links below

- INVOLVE

The CRN East Midlands are committed to Patient and Public Involvement and Engagement (PPIE). For further information please see the web links below

Patient and Public Involvement and Engagement (PPIE) in research

Patient and Public - I want to learn about research

Research that patients can be involved in

NIHR Involve

Local Host Site(s) Induction
Orientation to a new staff member's immediate work environment/host Trust is a key first stage in any induction programme. The CRN East Midlands Induction manual and e-Learning Package is intended to supplement the local Trust/organisation induction.

Glossary

http://www.invo.org.uk/resource-centre/jargon-buster/

Commonly Used Abbreviations			
A			
AE	Adverse Event	**AR**	Administration of Radioactive Substances Advisory Committee
ADR	Adverse Drug Event	**ATIMP**	Advanced therapy Investigational Medicinal Product
APR	Adverse Reaction		
C			
CA	Competent Authority	**CRN**	Clinical Research Nurse or Network
CAPA	Corrective Action and Preventative Action	**CRO**	Clinical Research Organisation
CI	Chief Investigator	**CSR**	Clinical Research Report
CRA	Clinical Research Associate or Agreement	**CTA**	Clinical Trials Authorisation or Trials Agreement
CRF	Clinical Report Form or Clinical Research Facility	**CTIMP**	Clinical Trials Investigational Medicinal Products
D			
DOH	Department of Health		
E			
EDC	Electronic Data Capture	**EU**	European Union
ETMF	Electronic Trial Master File	**EudraCT**	European Union Clinical Trials Database
F			

FDA	Food and Drug Administration	**FPFV**	First Patient First Visit
G			
GCP	Good Clinical Practice	**GP**	General Practitioner
GDP	Good Distribution Practice	**GPvP**	Good Pharmacovigilance Practice
GLP	Good Laboratory Practice	**GTAC**	Gene Therapy Advisory Committee
GMP	Good Manufacturing Practice		
H			
HEI	Higher Education Institute	**HRA**	Health Research Authority
HFEA	The Human Fertilisation Embryo Authority	**HTA**	Human Tissue Authority or Act
I			
IB	Investigator Brochure	**IRAS**	Integrated Research Application System
IDMC	International Data Monitoring Committee	**ISF**	Investigator Site File
IMP	Investigational Medicine Product	**ITT**	Intention to Treat
IR(m)ER	Ionising Radiation (Medical Exposure) Regulations	**IVRS**	Interactive Voice Response System
L			
LoA	Letter of Access	**LPLV**	Last Patient Last Visit
M			
MCTA	Model Clinical Trials Agreement	**MHRA**	Medicines and Healthcare Products Regulatory Authority
N			
NHS	National Health Service	**NIMP**	Non Investigational Medicinal Product
NIHR	National Institute for Health Research	**NRES**	National Research Ethics Service
P			
PD	Pharmacodynamics	**PIS**	Patient/Participant Information Sheet
PI	Principal Investigator	**PK**	Pharmacokinetics
PIC	Patient/Participant Identification Centre	**PV**	Pharmacovigilance
PIL	Patient/Participant Information Leaflet		
Q			
QA	Quality Assurance	**QC**	Quality Control
R			
R&D	Research and Development	**REC**	Research Ethics Committee
RC	Research Compliance	**RSI**	Reference Safety Information
S			
SADE	Serious Adverse Device Effect	**SOP**	Standard Operating Procedure
SADR	Serious Adverse Drug Reaction	**SSA**	Site Specific Assessment
SAE	Serious Adverse Event	**SSI**	Site Specific Information
SAR	Serious Adverse Reaction	**SUSAR**	Sudden Unexpected Serious Adverse Reaction
SmPC	Summary of Products Characteristics		
T			
TMF	Trial master File	**TSC**	Trial Steering Group
TMG	Trial Management Group		
U			
UKCRC	UK Clinical Research Collaboration	**USADE**	Unexpected Serious Adverse Device Event
V			
VHP	Voluntary Harmonisation Procedure		
W			
WHO	World Health Organisation		