Background

Acknowledgements
We gratefully acknowledge the hard work and effort made by all who contributed to the development of this learning resource, whether by writing, editing or peer reviewing, or in many cases participating in all three stages.

Development of this resource
This pack is reviewed on an annual basis and NES would like to thank the members of the Scottish Specialist Interest Group for Clinical Trials (CTSIG) and Rona Honnet, Principal Clinical Pharmacist, NHS Lanarkshire, for helping with the development of this resource.

Design
NES Corporate Communications team.

Disclaimer
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About this pack
Welcome to this educational package, which provides information about all aspects of pharmacy involvement in clinical trials within the NHS.

Clinical Trials provide vital evidence to support the safe and effective use of therapeutic interventions in modern medicine. At different stages of investigation of any medicinal product clinical trials are required to gain an understanding of the safe and effective doses that may be used in practice, the range and severity of anticipated adverse effects and the optimum place in therapy.

Clinical trials should only be conducted when the potential benefits outweigh any potential risks associated with the trial. At all times the safety and well-being of the trial participants must be fiercely protected. With this in mind the regulation of clinical trials is very tight and the conduct of trials closely scrutinised. The framework for practice in this area is constantly changing to reflect changes in the laws governing clinical trials.

This resource is aimed at pharmacists and pharmacy technicians who are involved in the conduct of clinical trials in any capacity. It is intended to help pharmacy staff to meet the legal requirements to be able to provide evidence of up to date training in Good Clinical Practice. It is also intended to provide practical guidance on all aspects of involvement in clinical trials.
Successful completion of this pack will not qualify you to act as a clinical trial specialist but it may confirm your interest in this aspect of pharmacy practice. Because legal requirements and best practice for clinical trials are reviewed and updated regularly it would be advisable to liaise with your local Clinical Trials Specialist Pharmacist if you anticipate close involvement in a clinical trial in your workplace. They will be able to advise you on the implementation of the guidance in this resource.

How this package can assist your CPD

At the beginning of each chapter the objectives describe what you should be able to do when you complete the particular chapter. This is designed to help you monitor how you are progressing through the pack and to identify any further learning needs that you may have in relation to each aspect. You should use your personal CPD record to record your learning, future learning needs and changes to practice that you have implemented as a result of your learning. If the information is not detailed in the pack we have also listed many useful reference websites which may provide you with the relevant information.

Keeping up to date

Although the information is as up-to-date as possible at the time of publication there is always new information available which is pertinent to your local situation in relation to clinical trials – you should contact your local Clinical Trials Specialist Pharmacist for local guidance. This is particularly important as clinical trials practice is continually being updated and changes are anticipated in 2013. You should also endeavour to continue to review recommended websites for further study.

Aims

The aims of this pack are to help you develop your knowledge and skills in relation to clinical trials and to support you to practice confidently and effectively in this area.

The package is designed to provide clear, up-to-date advice as well as providing you with many additional sources of useful information.
Objectives of the pack

The objectives of this pack are to support:

1. Awareness of the role of clinical trials in modern medicines
2. Awareness of the complexity of the current legislation and requirements of clinical trials
3. Awareness of the role of pharmacy staff in clinical trials practice.

Learning Outcomes

Completing this course will enable pharmacists and pharmacy technicians to:

- Describe the main phases and types of clinical trial and why they are used
- Describe the key elements of Good Clinical Practice
- Discuss the main legal and ethical requirements for clinical trials
- Discuss the main roles and responsibilities of pharmacy staff working in clinical trials
- Describe the principal roles of other professional bodies and individuals in running a clinical trial.

Feedback

We hope that you find this pack a useful update for you to provide pharmacy services in relation to clinical trials. Please help us to assess the value and effectiveness of the pack by feeding back any comments to us at NES below.

This course will take you approximately six hours to complete depending on your learning style and experience. It is best to work your way through the chapters from the beginning to the end in logical order. However you may wish to focus on particular chapters that are relevant to your practice.
chapter 1

Introduction and Background to Clinical Trials
This chapter introduces the idea of clinical trials, covering their development from the simple concept to the complex forms used today. The different types and phases of modern clinical trials are discussed and the principles of good clinical practice introduced.

Objectives:
- To understand the concept of clinical trials
- To be aware of the history of clinical trials
- To understand the different types of clinical trials
- To understand the different phases of clinical trials
- To be aware of the principles of Good Clinical Practice (GCP).

Introduction
Clinical Trials are used to discover new medicines and treatments which will benefit patients and their conditions. The basis for conducting a clinical trial is that there must be some likely benefit from doing so and that any potential risks associated with the trial are outweighed by the potential benefits. All licensed medicines today require a marketing authorisation prior to their release into the general market for use by healthcare professionals and patients. Prior to this release, medicines must undergo rigorous testing firstly in a laboratory, then on animals and then on humans in the form of a clinical trial to ascertain the safety and efficacy of the medicine. The fact that treatments are new does not always mean that they are more effective than existing therapies. Clinical trials are the best way to assess whether new treatments are safe, what side effects they have and whether they work better than the existing standard treatment. Clinical trials have also shown ways to use existing treatments differently, to help people suffering from life threatening illnesses to live longer and to experience a better quality of life. The primary aim in clinical trials is to protect the rights, safety and wellbeing of the clinical trial participants.

Unfortunately, history shows that patient welfare was not always such a high priority.

History of clinical trials
The earliest recorded clinical trial is documented in the Old Testament, and describes how Daniel followed a diet of pulses and water instead of the meat and wine recommended by King Nebuchadnezzar II. Daniel remained healthy while his companions became ill, convincing Nebuchadnezzar to change his mind.

Most people think of James Lind as the father of clinical trials, since he was the first to introduce control groups into his experiments. In this manner, he documented the fact that citrus fruits in the diet could prevent scurvy. Lind carried out trials while at sea on board the Salisbury in 1747. All scurvy patients were given the same general diet but this was supplemented with various additional items, including cider, elixir vitriol, vinegar, seawater, nutmeg and (crucially) oranges and lemons. In just six days, those patients taking citrus fruits were fit for duty concluding that citrus fruit prevented scurvy.

Modern clinical trials
From 1800 onwards, clinical trials began to proliferate and more attention was paid to study design. Placebos were first used in 1863, and the idea of randomisation was introduced in 1923.

The first trial using properly randomised treatment and control groups was carried out in 1948 by the Medical Research Council, and involved the use of streptomycin to treat pulmonary tuberculosis. This trial also featured blind assessment (where neither the researchers nor the patients knew which treatment group each patient was in at the time of the study) enabling unbiased analysis of the results.

Since 1945, the ethical impact of clinical trials has become increasingly important, resulting in strict regulation of medical experiments on human
subjects. These regulations have been enshrined in documents such as the Nuremburg Codex (1947) and the Declaration of Helsinki (1964, amended in 1975, 1983, 1989, 1996, 2000 and 2001).

The most recognisable of these is probably the Nuremburg code which came into effect in 1947 after the Nuremburg trials where 23 Nazi doctors were tried in court for conducting experiments on concentration camp victims. These experiments included involuntary euthanasia, sterilisation, wound healing and high altitude sickness to name but a few.

The Nuremburg trials had a great effect worldwide as people were shocked by the horrific things carried out by doctors in the name of medical research. From this the Nuremburg code was developed and consisted of 10 points. Central to this was the need for informed consent. This means that no-one can be forced to participate in human experiments and all participants must understand the potential risks that they are undertaking. The Nuremburg code became the prototype for future regulations.

Clinical trials have thus evolved into a standard procedure, focusing on patient safety and requiring informed consent from all participants. There will always be a balance between medical progress and patient safety, and the regulation of clinical trials helps to ensure that this balance is acceptable.

Clinical trials today

What do clinical trials involve today?

Before we go into detail, let us consider the definition of a clinical trial.

A clinical trial, as defined by the Medicines Act of 1968 is:

‘An investigation or series of investigations consisting of the administration of one or more medicinal products where there is evidence that it may be beneficial to the patient by one or more doctors or dentists for the purpose of ascertaining what effects, beneficial or harmful the product(s) have.’

In other words we are looking for the most appropriate treatment for future patients with a specific medical condition.

What factors must be in place to conduct a clinical trial?

![Components of a clinical trial](image)
Sponsor and Approvals

All Clinical trials require a Sponsor who is an individual, company, institution or organisation which takes overall responsibility for the initiation, management and/or financing of a clinical trial. The Sponsor can be a Pharmaceutical company, hospital board or university and is responsible for:

- Obtaining regulatory and ethical approval from the MHRA and Research Ethics
- Ensuring Good Clinical Practice (GCP) and trial conduct
- Trial monitoring and audit
- Pharmacovigilance
- Indemnity in case something goes wrong and the subject is injured or worse dies as a result of the study.

Most clinical trials today are sponsored by large pharmaceutical companies and this research is called commercial research. Clinical trials sponsored by hospital trusts, charities or universities are called non-commercial research.

Investigator

The investigator is an authorised health professional who is responsible for the conduct of the study and the study team at the trial site. They can delegate certain roles and tasks to other health care professionals who must receive training in GCP. They must ensure patients in the trial are managed according to the trial protocol and report any serious adverse events (SAE) to the sponsor.

Protocol

Clinical trials are conducted in accordance with a clinical trial protocol. A protocol is a study plan in which all clinical trials are based and describes in detail how the study is to be undertaken. It may contain a few pages, e.g. for a non-commercial study, to over 200 pages for a commercial study. Clinical trial protocols must adhere to accepted standards of safety, patient care and data interpretation.

Drug treatment

Drugs used in clinical trials are called Investigational Medicinal Products (IMPs) and this is a pharmaceutical form of an active substance or placebo being tested or used as a reference. These can include existing marketed products used in a different way from their authorised licence or used in an indication not listed on the marketing authorisation; others will be completely new medicines or formulations.

Pharmacy staff must ensure that accountability records are kept for these products and it is very important these logs are accurate, legible, up to date and contain all relevant information for providing a robust audit trail of the IMP.

Trial design

How is bias avoided?

Randomisation is the key to avoiding bias. In order to reduce bias subjects will be randomly assigned to a treatment. This process is predetermined either as a 1:1 ratio or in some instances more subjects will be allocated to the active trial group to enable more information about the drug to be assimilated. Treatments may be allocated in several ways e.g. via a list where subjects will be allocated to active treatment or placebo treatment at random or as with most commercial trials randomisation via a computerised system.

Control – what types of treatment are subjects given?

Subjects will often be entered into an active group or a control group. The control group provide the yard stick against which the efficacy and safety
of the study drug will be measured. The control in a prospective study controls the sources of variability due to the situation. This enables any differences between the control and active group to be attributed to the trial drug and not another variable.

In a placebo controlled trial subjects will either receive the active trial drug or will receive an inactive placebo instead. The placebo ‘drug’ should look identical to the active drug to reduce any bias by the investigator or subject.

**Blinding**

There are several options for blinding a clinical trial in order to reduce bias:

- **Open label**: both the patient and the investigator are aware of the drug being administered
- **Single blind**: the patient is not aware of the drug being administered
- **Double blind**: both the patient and the investigator are not aware of the drug being administered.

**Types of trial design**

The most common trial designs are:

- **Parallel**: patients receive the assigned treatment arm and both arms of the study are tested at the same time
- **Cross over**: each patient receives a course of each of the treatments being studied i.e. they ‘cross-over’ to the other after a defined period.

**Patients (‘Subjects’)**

Why do patients participate in clinical trials?

- To gain access to new research treatments before they are widely available
- To play a more active role in their own healthcare
- To contribute to medical research
- To obtain expert medical care at health care facilities during the trial.

**Who can participate in a clinical trial?**

Subjects can be entered into a clinical trial if they meet certain criteria as specified in the protocol. The factors that allow subjects to participate in a clinical trial are called ‘inclusion criteria’ and those that disallow subjects from participating are ‘exclusion criteria’. These criteria are based on many factors e.g. age, gender, the type and stage of a disease and previous treatment history. It is important to note that inclusion and exclusion criteria are not used to reject appropriate subjects but to identify appropriate subjects and to keep them safe.

Before participating in a clinical trial they must sign a consent form and entry into trials must be on a voluntary basis. This in known as informed consent and is the process of learning the key facts about a clinical trial before deciding whether to participate or not. Doctors and nurses involved in the trial inform the subject about the details of the study, including the risks and potential benefits, treatment involved and the duration of the study. All subjects are made aware that they can withdraw from the study at any time.

**How long do clinical trials last for?**

The duration of a study will be influenced by the illness being treated. Some studies are relatively short and others can be active for many years as subjects are followed up to assess their well-being.
Phases of clinical trials

Clinical trials are referred to in ‘phases’ and depending on how much is known about the drugs involved determines the study phase. There are 4 phases of clinical trials. The trials at each phase have a different purpose and help scientists answer different questions. Throughout all phases of clinical trials subjects will be closely monitored for side effects or adverse reactions.

Assume we have discovered a new compound that has shown promising activity in animal studies – it will need to be tested in humans so the first step is a phase 1 trial.

Phase 1 trials
- First experiment in humans conducted in healthy volunteers or patients depending on the type of IMP
- Small number of subjects (between 20-80)
- Primarily concerned with dose finding, drug safety, tolerance, side effects, absorption, distribution, metabolism and excretion
- Subjects are given increasing doses of the drug which will determine the maximum tolerated dose and will highlight if the therapeutic dose may be exceeded.

If the results are favourable at the end of phase 1, a phase 2 trial will commence.

Phase 2 trials
- Conducted in patients who have the actual disease
- Small number of patients but more than a phase 1 study (100-200)
- Primarily concerned with establishing dose levels, safety and efficacy in the indicated disease.

If the results of a phase 2 trial indicate that a new treatment may be as good as the existing treatment, or better, then the drug will be trialled in a phase 3 study.

Phase 3 trials
- Large number of subjects are recruited in many hospitals in the UK and abroad (can be 1000s)
- Compare new drug to existing standard treatment
- Full scale evaluation of treatment
- Produces bulk data for marketing authorisation application.

At the end of a successful programme of phase 3 studies there should be enough safety data to apply for a marketing authorisation.

Phase 4 trials
- For a drug that has received product license
- Extensive post marketing surveillance-allow clinicians to gain experience of a new drug under controlled conditions
- Ascertain long term risks and benefits.

Good Clinical Practice (GCP)

As clinical trials involve human subjects, there are many laws, directives and regulations in place to protect the subject’s safety and ensure the data is valid. One of these directives is the EU Directive 2001/20/EC Good Clinical Practice in Clinical Trials which was implemented in the UK in the form of the Medicines for Human Use Act 2004. Encompassed in the new legislation was the setting of Good Clinical Practice (GCP) standards.

Good Clinical Practice (GCP) can be defined as:

An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and that the clinical trial data is credible. GCP is a legal requirement in the UK and indeed around the world and is accepted as the required standard for conducting clinical trials on investigational medicinal products.
There are 14 principles of Good Clinical Practice as outlined in the table below:

### 14 Principles of Good Clinical Practice (GCP)

<table>
<thead>
<tr>
<th>Rights, safety and well-being of trial subjects shall prevail over science and society</th>
<th>The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his/her tasks</td>
<td>All clinical information recorded, handled and stored in a way that can be accurately reported, interpreted and verified while confidentiality remains protected</td>
</tr>
<tr>
<td>Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects</td>
<td>Anticipated benefits justify risks</td>
</tr>
<tr>
<td>The necessary procedures to secure the quality of every aspect of the trial must be complied with</td>
<td>Medical care and medical decisions shall always be the responsibility of a qualified doctor or dentist</td>
</tr>
<tr>
<td>The necessary clinical and non-clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial</td>
<td>Trial initiated only if ethics committee and licensing authority conclude that anticipated therapeutic and public health benefits justify risks. Continued only if compliance with this is permanently monitored</td>
</tr>
<tr>
<td>Clinical trials will be conducted in accordance with principles in the Declaration of Helsinki</td>
<td>Rights of each subject to physical and mental integrity, to privacy and to protection of data concerning him in accordance with Data Protection Act are safeguarded</td>
</tr>
<tr>
<td>The protocol shall provide for the definition of inclusion and exclusion of subjects… monitoring and publication policy</td>
<td>Provision made for insurance and indemnity to cover liability of investigator and sponsor in relation to clinical trial</td>
</tr>
</tbody>
</table>

Table 1

**Principles of Good Clinical Practice**

It is a mandatory requirement that all staff who are involved in clinical trial work comply with GCP. Staff must be able to demonstrate through training and education that they understand the principles of GCP. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected and that the results of clinical trials are credible and accurate.

References are provided at the end of this pack - click here.
chapter 2

The Legal Framework
This chapter introduces the relevant legislation, regulation and guidance for the conduct of clinical trials starting with the European ‘Clinical Trials Directive’. The Declaration of Helsinki also details the ethical principles for clinical trials and research governance.

Objectives:
- To be aware of the key legislation and guidelines for conducting clinical trials
- To be aware of the role of the MHRA in UK clinical trials
- To be aware of the main differences between trials of ATMPs and other IMPs
- To be aware of the key ethical and governance issues for clinical trials.

European Directive 2001/20/EC is often referred to as the ‘Clinical Trials Directive’. This EU wide legislation introduced a single approach to the legislation underpinning the conduct of clinical trials in the European Union. The EU Directive defined a clinical trial as:

‘Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.’

EU Directive 2001/20/EC was transposed into UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004 which became UK law on 1st May 2004. This legislation applies to the conduct of all clinical trials whether commercially or non-commercially funded, single or multi-site. The Medicines for Human Use (Clinical Trials) Regulations meant that for the first time:

- Pharmacology studies in healthy human volunteers (Phase 1 studies) required authorisation from the MHRA (the UK Competent Authority) where previously they only needed a favourable opinion of an ethics committee
- Investigational medicinal products (IMPs) had to be manufactured to good manufacturing practice (GMP) standards and that the manufacturer must hold a Manufacturing Authorisation which is often abbreviated to MA IMP
- Each trial must have an identified sponsor who takes responsibility for its initiation, management and conduct. The Regulations allow a group to collaborate e.g. an NHS Board and a University.

Other aspects of clinical trials that had previously been guidance, became a legal requirement for the first time such as establishing a statutory basis for ethics committees and competent authority review, the requirement to conduct clinical trials in accordance with principles of Good Clinical Practice (GCP) and for inspections by the MHRA on GCP and GMP compliance with enforcement powers. Since the EU Directive 2001/20/EC was first introduced there have been further revisions which in turn have meant changes to the UK regulations.

For further information click here.
Detailed information on clinical trials:

1. EudraLex - Volume 10 Clinical trials guidelines

Eudralex volume 10 is a suite of guidance documents which provide in-depth information on various aspects of clinical trials. Eudralex volume 10 contains 6 main chapters with guideline documents for a broad range of clinical trial related activities. These are updated on an ongoing basis and are an excellent resource on detailed information relating to the expected standards for clinical trials. Chapters I and III provide detailed guidance on submission to Competent Authorities, and quality of Investigational Medicinal Products respectively. These are likely to be of most interest to senior clinical trial pharmacy staff particularly those who are acting on behalf of the sponsor. Chapter V also contains guidelines on Good Clinical Practice and on Advanced Therapy Medicinal Products (ATMPs) which are also very relevant to current pharmacy practice.

Click here for further information.

2. The UK Competent Authority - MHRA

The Medicines and Healthcare products Regulatory Agency (MHRA) as the UK Competent Authority review submissions for proposed clinical trials. The MHRA Clinical Trial Authorisation form is an integral part of the IRAS form. Detailed guidance is provided by the MHRA of how and what should be submitted. The MHRA have also developed a number of resources to help researchers understand the processes involved in initiating and conducting a clinical trial. These include:

- **Algorithm** to help identify if a study is a clinical trial or non-interventional research activity
- **Examples** to help illustrate if a medicine in a clinical trial is an IMP or a NIMP (non-investigational medicinal product)
- Information on contraceptive and QT interval assessment requirements
- **Frequently asked questions** and mock applications.

**Risk adaptive approach**

In April 2011 the MHRA adopted a ‘risk adaptive approach’ for UK trials as permitted within the legislation. What this means in practice is that the initiation, management and monitoring of clinical trials can vary depending on the level of risk. The level of risk is largely related to how much is known about the investigational medicinal product and whether the potential risks associated with the trial are no higher, somewhat higher or significantly higher than standard medical care. In practice the marketing authorisation status is used as an indicator. Type A studies can be submitted to the MHRA under the Notification Scheme which results in a faster response. Studies with off-label use (such as in paediatrics and oncology, etc) may be classed as Type A if the off-label use is established practice and supported by sufficient published evidence and/or guidelines. Type B and Type C studies are required to go through the full submission process.

![Risk Adaptive Approach](image_url)

**Figure 2**

**Risk Adaptive Approach**

<table>
<thead>
<tr>
<th>Lower Risk (Type A)</th>
<th>Higher Risk (Type C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Researcher plans a clinical trial using a UK licensed medicinal product where it will be used in accordance with the licensed indication, dose and form.</td>
<td>Researcher plans a clinical trial using a novel investigational medicinal product with only very limited information on use in humans.</td>
</tr>
</tbody>
</table>
Inspection
The MHRA conduct GCP inspections in the UK. There are three types of inspection:

- Routine inspections are inspections of the systems and procedures used to conduct clinical research in the UK by commercial and non-commercial organisations, in order to assure compliance with applicable legislation. Organisations are notified of routine inspections in advance.
- Triggered inspections: these are ad-hoc inspections that may be triggered as a result of GCP or other regulatory violations or in the case of commercial companies, MHRA licensing requests. Generally the organisation will receive some advance notice, but the MHRA can choose to inspect without providing notice.
- Committee for Medicinal Products for Human Use (CHMP) requested inspections can arise from central marketing authorisation (MA) submissions: The European Medicines Agency (EMEA) coordinates these inspections. These will generally apply to commercial organisations.

After receiving notice of intention to inspect, the MHRA will require the submission of a GCP inspection dossier, the content of which is defined by the MHRA and includes a list of clinical trials, standard operating procedure lists, organisational charts and overview of facilities. Based on this, the MHRA will determine the resource required and plan the visit. Further information on inspection process is provided by the MHRA and the NHS R&D Forum has guidance on preparing for inspection. At the end of the inspection visit the inspector(s) will relay back their findings classed as ‘critical’, ‘major’ or ‘other’. This is then followed up by a formal report. The organisation is asked to provide a formal response and once an adequate response is agreed with the inspectorate, a closing letter and GCP Inspection Statement is issued.

3. Voluntary Harmonisation Procedure
In 2009, the Voluntary Harmonisation Procedure was introduced. This allows sponsors of multi-national trials to submit a core set of documents which are reviewed by all the National Competent Authorities involved. The sponsor then receives a single response letter. The VHP process has the potential to minimise the time involved in conducting multinational research and provides a one-stop point of assessment.

4. Advanced Therapy Medicinal Products
Advanced Therapy Medicinal Products (ATMPs) are defined under Directive 2001/83/EC and include:

- Gene therapy medicinal products. Through a manufacturing process, a target therapeutic gene is inserted into a delivery system known as a vector. Vectors can be viral e.g. an adenovirus or they can be non-viral delivery systems. The hope is that the target therapeutic gene, once delivered, will be expressed \textit{in vivo} i.e. in the body.
- Somatic cell therapy is when autologous, allogeneic, or xenogeneic living cells which have been manipulated or processed \textit{ex vivo}, are administered to humans of e.g. stem cells. It does not include e.g. blood transfusions.

The first ATMP to receive a Marketing Authorisation in Europe was ChondroCelect and there is now an increasing number of clinical trials being conducted with ATMPs. There are differences in the regulatory requirements for submission of clinical trials in ATMPs and studies are reviewed by the Gene Therapy Advisory Committee (GTAC) which is a national ethical committee. These clinical trials offer new challenges for pharmacy services but there is guidance information available from the Health and Safety Executive and the European Association of Hospital Pharmacists. The EMA have also produced detailed guidelines on GCP specifically in relation to ATMPs.
Declaration of Helsinki
The Declaration of Helsinki was first adopted in 1964. It has undergone a number of revisions as medical science and ethical problems have evolved, but at its heart, it covers fundamental principles for medical research involving human subjects such as safeguarding of research subjects, informed consent, risk minimisation and the requirement to adhere to an approved research protocol.

Research Governance
Research Governance is concerned with setting standards to improve the quality of research and to safeguard the public. The focus of research governance is to promote good practice and work to improve ethical and scientific quality of research. Ensuring that lessons are learned from incidents and preventing poor performance and misconduct in research are also important. The principals of research governance apply to all research and not just clinical trials of investigational medicinal products.

Guidance and Useful Links
There is now a significant number of authoritative web resources to support the conduct of clinical trials in the UK. These are given at the end of the pack grouped under key themes. There are relatively few resources aimed specifically at pharmacy staff although various organisations are working to increase the direct support available to pharmacy staff.
Click here to go to guidance documents.
chapter 3

Hosting and Sponsoring a Clinical Trial
3.1 Getting Started

This section looks at the process of setting up a clinical trial from obtaining funding and sponsorship for a proposed trial through the various stages of the approval process.

Objectives:
- To understand the cost considerations for the conduct of clinical trials within the NHS and how they are funded
- To understand how a trial is granted legal and ethical approval to proceed.

Is the proposed study research, service evaluation or audit?
One of the first decisions that needs to be made by the researcher is whether their proposed study is in fact research. While all clinical trials fall under the auspices of research the line can be more blurred for proposals which are evaluating elements of standard NHS services. This is an important decision as only proposals which are judged to be research require ethical review by a Research Ethics Committee and R&D Approval. The National Research Ethics Service (NRES) have produced useful guidance although help can always be obtained from local R&D or from the NRES service.

Funding of Clinical Trials
Consideration needs to be given to funding sources for all research prior to starting. For non-commercial organisations like the NHS, conducting a clinical trial can be expensive with major costs including research staff and data management costs. Equipment, laboratory and sample shipping costs can also be substantial. Obtaining medicines in a suitable format for use in a clinical trial can also be expensive and costs for manufacture, including blinding, QP release and final shipment can quickly mount up. The majority of non-commercial clinical trials are now funded via a grant that the researcher has to apply for. Many R&D offices require that grant submissions must be reviewed prior to them being submitted to the funders for consideration. If a grant is awarded but fails to cover all the necessary costs then there is the real danger of the research either being delayed or indeed not being able to start due to insufficient funds.

The grant award process is usually competitive and potential funders will generally look at scientific quality, the proposed research question and how it fits with the aims of the awarding organisation, value for money and potential impact of the research. Grants may be awarded by charities e.g. Cancer Research UK or by government funded organisations such as the Chief Scientist Office (Scotland) or NIHR (National Institute for Health Research).
The grant needs to cover certain core research activities, however the NHS is also required to support research as an integral part of NHS activity. Detailed guidance on who funds what in non-commercial research has recently changed and Scotland has now joined England and signed up to AcoRD (attributing costs of research and development). Commercial organisations conducting research within the NHS are expected to cover the associated research costs. These costs can be calculated using the NIHR Industry Costing Templates which include pharmacy costs.

Sponsorship

All research that takes place in the NHS must have a sponsor. The sponsor is the individual, or organisation(s) that takes responsibility for confirming there are proper arrangements to initiate, manage, and finance of the research. Sponsors have specific legal duties under the Medicines for Human Use (Clinical Trials) Regulations 2004. Normally, the sponsor will be one of the organisations taking the lead for particular aspects of the arrangements for the study and may be the Chief Investigator’s employing organisation, the lead organisation providing healthcare, or the main funder. The latter is generally the case for commercial research.

The NHS can act as sponsor for the purposes of clinical trials as can a university and indeed there are models where the NHS and University may act as co-sponsor for a clinical trial. Prior to taking on the role of sponsor, non-commercial organisations will generally have a process to review the potential risks associated with the study to ensure there will be sufficient resources within the organisation to support the study. As part of the risk assessment, the researchers may be asked to amend or adapt their initial proposals so as to minimise potential risks to patients, the organisation or financial outlay. Agreement to act as sponsor cannot be assumed and confirmation of sponsorship must be provided in writing.

IRAS (Integrated Research Application System)

Once the fundamental issues of funding and sponsorship etc. are dealt with, the next stage is to obtain the appropriate approvals. All clinical trials require the following:

- Medicines and Healthcare products Regulatory Agency (MHRA) Clinical Trial Authorisation
- NRES Research Ethics Committee (REC) favourable opinion
- Local NHS R&D approval.

However other approvals may also be required depending on the individual requirements of the research. IRAS is a web-based system that captures the information required for approval of all health and social care/community care research in the UK including clinical trials. Using filter questions, the system collates the data required for submission to each of the relevant bodies. The IRAS forms can also be transferred to different users. For example, the researcher could transfer the MHRA Clinical Trial Authorisation (MHRA CTA) form to pharmacy staff to complete or to review prior to submission. An e-Learning module is available.

The requirements for research submissions vary across the UK as there are legislative differences between the devolved nations and England but this is incorporated into the IRAS. Focusing on requirements for clinical trials, submissions to the following bodies are also covered by IRAS:

- Administration of Radioactive Substances Advisory Committee (ARSAC): required for administration of radioactive medicinal products
- Gene Therapy Advisory Committee (GTAC): is a UK national research ethics committee for clinical trials of gene therapy, other advanced therapy medicinal products and certain other types of research.

In order to obtain the above approvals, the researcher/sponsor of the clinical trial need to demonstrate various requirements and safeguards are in place.
**Ethics**

Fundamentally, the National Research Ethics Service in the UK exists to:

- Protect the rights, safety, dignity and well-being of all research participants
- Facilitate and promote ethical research that is of potential benefit to participants, science and society.

The Research Ethics Committee is entirely independent of the sponsor, funders and investigators. The participant, their expected level of commitment/involvement in research and potential for exposure to harm are all considered as part of the ethical review process.

There are two types of Research Ethics Committee – ‘recognised’ and ‘authorised’. Only ‘recognised’ committees may review clinical trials of investigational medicinal products (CTIMPs) in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004. There are two types of recognised RECs:

- Type 1 RECs review Phase 1 CTIMPS in healthy volunteers only
- Type 3 RECs review CTIMPs (other than phase 1 trials in healthy volunteers) and all other research taking place in more than one domain anywhere in the United Kingdom. They can also review other research.

Authorised committees may review all applications except CTIMPs. Both recognised and authorised work to the standards outlined by GAfREC.

**Application for Ethics Approval**

All submissions for REC review must be submitted from IRAS following the prompts on the system. The exact requirements for submission will differ depending on the proposed research but the main points of inclusion for a CTIMP are shown in Table 2.

<table>
<thead>
<tr>
<th>Typical Requirements for submission for ethical approval</th>
</tr>
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<tbody>
<tr>
<td>- Cover letter</td>
</tr>
<tr>
<td>- REC application (Parts A-D of the IRAS form)</td>
</tr>
<tr>
<td>- Research protocol</td>
</tr>
<tr>
<td>- Investigator's brochure and/or Summary of Product Characteristics as appropriate</td>
</tr>
<tr>
<td>- Summary CV for Chief Investigator</td>
</tr>
<tr>
<td>- Research participant information sheet (PIS)</td>
</tr>
<tr>
<td>- Research participant consent form</td>
</tr>
<tr>
<td>- Letters of invitation to participant</td>
</tr>
<tr>
<td>- GP/consultant information sheets or letters</td>
</tr>
<tr>
<td>- Evidence of insurance or indemnity (non-NHS sponsors only)</td>
</tr>
<tr>
<td>- Letter from sponsor and statistician</td>
</tr>
<tr>
<td>- Referee's or other scientific critique report</td>
</tr>
<tr>
<td>- Details of any Data Monitoring Committee</td>
</tr>
<tr>
<td>- Sample diary card/ patient card</td>
</tr>
<tr>
<td>- Validated/non-validated questionnaire</td>
</tr>
<tr>
<td>- Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website</td>
</tr>
</tbody>
</table>

Table 2

**Ethics Submission for a CTIMP**

In order for the application to reviewed, it has to be booked into the relevant Ethics Committee. Depending on the type of application and whether the researcher wishes the convenience of having the review conducted locally, booking can be done either centrally via the Central Allocation System or directly via the local committee. Only one ethical review is required for the whole of the UK.
RECs are scheduled to meet on a monthly basis to ensure that decisions can be made to a sixty day clock. The 60 day timeline starts on the day the REC takes receipt of a valid application. If an application is incomplete, the 60 day clock only starts once the complete document set is obtained. Applicants are able to attend the part of the REC meeting where the application is discussed and this can be very useful to the ethics committee and the investigator as it allows the researcher to answer questions directly to the committee on the ethical issues and for the investigator to understand any potential ethical concerns raised by the committee.

The REC decision is provided in writing within 10 working days after the meeting and contains details of any revisions or clarifications required by the REC. There are four potential outcomes:

- Final opinion: favourable
- Final opinion: unfavourable
- Provisional opinion – with request for further information, clarification or revision. The 60 day clock stops until the committee are provided with the requested information from the researcher.
- No opinion – gone to referee for consultation before opinion given.

A flow chart is available that describes the application process.

**MHRA Clinical Trial Authorisation**

All clinical trials including those submitted under the Notification Scheme require submission of the Clinical Trial Application to the MHRA along with supporting documentation. IRAS populates the application form with information on the protocol, applicants’ details etc. from the main IRAS dataset. Specific information required is shown in table 3.

<table>
<thead>
<tr>
<th>Specific Information Required</th>
<th>Supporting Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type of IMP e.g. chemical, biotechnological, advanced therapy etc.</td>
<td>• Covering letter</td>
</tr>
<tr>
<td>• Use and composition of any placebos</td>
<td>• Protocol</td>
</tr>
<tr>
<td>• Licensing status of proposed IMPs</td>
<td>• Investigator’s Brochure or SmPC</td>
</tr>
<tr>
<td>• Use of the IMP in previous clinical trials by the sponsor</td>
<td>• IMPD/simplified IMPD</td>
</tr>
<tr>
<td>• Dosing information including maximum treatment duration, dose and treatment duration for each IMP</td>
<td>• NIMP Dossier (if required)</td>
</tr>
<tr>
<td>• Details of manufacturer or importer providing the final QP release</td>
<td>• Labelling content of the IMP or justification for its absence. (Note: only the text content is required. A mock-up of the label is not a requirement for submission)</td>
</tr>
<tr>
<td>• MedDRA codes used to classify research into different therapeutic areas</td>
<td>• Manufacturer’s authorisation for each manufacturing site or Importer’s authorisation plus QP declaration on GMP for each manufacturing site.</td>
</tr>
<tr>
<td>• Scope and phase of the clinical trial</td>
<td></td>
</tr>
</tbody>
</table>

Table 3

**MHRA Clinical Trial Application Submission**

Detailed guidance on requirements for submission for EU competent authorities available and the MHRA website also provides further information. Submissions to the MHRA have to be made in a specific format. The MHRA have a fee structure for submissions depending on the phase of the study with phase 1 studies attracting the highest fee. An annual maintenance fee is also charged.
The MHRA will provide their initial assessment within 30 days although application for phase 1 healthy volunteer studies will be assessed and processed within an average of 14 days or less. Submissions made under the Notification Scheme will receive a notification letter stating that the trial may go ahead after 14 days from receipt of the notification if the MHRA has not raised any objections.

There are three possible outcomes from MHRA submission:

- Acceptance of the request for a clinical trial authorisation
- Acceptance of the request for a clinical trial authorisation subject to conditions
- Grounds for non-acceptance of the request for a clinical trial authorisation.

The MHRA response letter should be carefully reviewed either to ensure that the conditions are indeed met or if non-acceptance the reasons provided and the timescales within which the response must be made. Non-acceptance letters are now e-mailed to applicants. Generally, the response must be resubmitted to the MHRA within 14 days otherwise the application will be rejected and the application process has to be made again complete with fees.

Within the EU, the Competent Authority is required to upload data on approved clinical trials to the EudraCT database. A sub-set of this information including the sponsor, study title and therapeutic area is visible on the EU Clinical Trials Register website which is searchable and accessible to all.

**R&D Management Approval**

Researchers must obtain R&D Management approval prior to commencing any research activities and this includes the conduct of clinical trials. The R&D management approval process looks to ensure that all governance requirements are met prior to the study starting. For a clinical trial that is sponsored by the same organisation, it’s likely that the local NHS R&D department will already have been heavily involved in the study leading up to the grant submissions, ethics and MHRA submissions. Of course, every NHS organisation hosts research and clinical trials sponsored by both commercial and non-commercial organisations. All submissions for multi-site research regardless of who is the sponsor for the study is managed in Scotland by NHS Research Scotland Permissions Coordinating Centre (NRS Permissions CC) based in Aberdeen. The NRS Permissions CC collates the required submission documents uploading them to SReDA the Scottish Research Database Application, where authorised R&D department staff can then access the documents. NRS Permissions CC also liaises with the equivalent bodies in England, Wales and Ireland. A different document set is required for commercial and non-commercial organisations in Scotland. NHS Permissions CC and local R&D offices work to a 30 day timeline. The clock starts once a complete document set is in place. The clock can stop for a number of reasons, for example while awaiting a response to a query from the research organisers or whilst contracts are being signed.

R&D departments are heavily involved in ensuring that contracts are in place to cover the various elements of the proposed research. These are legal documents that formalise the relationships between funders, industry and other research and academic institutions. In order to simply the review of these agreements R&D and industry have developed standard model clinical trial agreements (mCTA) for use in Scotland. Model agreements have also been developed for non-commercial research in the NHS. While information on the individual study still needs to be entered with information tailored to the study requirements in the appended schedules, the expectation is that the main content is used without modification. The agreements outline responsibilities for the sponsor and the NHS organisation and provide the legal basis on which any disputes will be settled.

In addition to submitting documents to NRS Permissions CC, a Site-Specific Information (SSI) is required. The SSI is generated via IRAS.
and allows the local R&D office to review the suitability of the local resources to support the research. The SSI needs to be submitted to each participating Health Board in a clinical trial. The SSI, also covers the permissions of support department such as pharmacy.

Once the appropriate approvals are in place, the local R&D management office will issue a R&D management approval letter. Again, it is important that the letter is carefully reviewed as it will list expected requirements for the conduct of the research.

**Post approval**

Once the relevant approvals are obtained, the relevant bodies need to be informed of any proposed changes. Changes to the research may be non-substantial or substantial. There are differences in what constitutes a substantial amendment for clinical trials for ethics purposes compared to the MHRA and it is possible for a change to require a substantial amendment to ethics but for this not to constitute a substantial amendment to the Competent Authority. Sponsors are ultimately responsible for deciding if a proposed amendment is substantial or not, but detailed guidance is provided by both ethics and the MHRA. Proposed amendments will also need R&D review prior to their implementation to assess potential impact on financial and local conduct of the research.

Once a clinical trial is completed, ethics and the MHRA must be formally notified using the Notification of the End of a Clinical Trial of a Medicine for Human Use to the Competent Authority and the Ethics Committee. This is a sponsor’s responsibility and must be completed within 90 days of the planned research finish (as defined by the study protocol) or within 15 days if the study is terminated early.
3.2 Pharmacy sponsor support roles

This section looks at the role of pharmacy staff in supporting clinical trials that are sponsored rather than hosted by the NHS.

Objectives:
- To be aware of the roles of pharmacy staff at different stages of a clinical trial
- To be aware of the safety and quality issues with IMPs.

The involvement of pharmacy services when a clinical trial is hosted by an NHS Board or Trust is generally well established. However, the input of pharmacy staff when the NHS Board/Trust is sponsor for a clinical trial is more variable. Local arrangements may differ, but there follows a short overview of some areas where pharmacy may usefully contribute to the development of locally sponsored clinical trials.

Protocol development
In order to minimise potential delays later on, pharmacy should ideally participate at the earliest stages in protocol development. Pharmacy staff can provide advice on ensuring that there is sufficient information in the protocol and/or supporting documentation to allow the safe administration of IMPs or NIMP to patients and to ensure that they comply with current regulatory and good practice requirements.

By definition of being a research study, there is likely to be limited information available on the use of the medicine in the particular clinical context. There must be sufficient evidence and/or monitoring available to justify the proposed dosing regime as at the heart of each clinical trial is the need to ensure there is a positive risk-benefit assessment for those patients participating in the study. The Summary of Product Characteristics or Investigator's Brochure will provide key information on clinical use of the medicine. A comprehensive clinical review of the protocol at this stage may also highlight potential gaps in the protocol or areas that conflict with current practice. The pharmacy review may incorporate the following:
- Dose/cumulative dose
- Route, frequency and duration of administration
- Safety of the medicine and any excipients in the patient group to be studied
- Proposed administration form
- Review of safety warnings and good practice statements from national and local organisations e.g. NPSA
- Contra-indications, cautions in use, interactions against the proposed protocol inclusion/exclusion criteria
- Clinical monitoring required
- Interactions between study medicines and previous or concomitant medicines
- Potential adverse reactions
- Impact of the research on current practice – what is the potential for use of the IMP to lead to confusion/errors?

Involvement in research should not generally mean that patients are denied pharmaceutical services that they would normally receive as part of their normal care as a result of entering into a study such as therapeutic drug monitoring. Where local or national safety or good practice statements have been issued, it is important that the research should conform to these standards. Any deviations should be appropriately justified and documented.

Sourcing of IMPs and quality related aspects
All IMPs, NIMPs and other medicines administered to patients in the context of research eg. inert tracers, must be of an appropriate quality and evidence of quality standards having been met must be available.
IMPs and NIMPs should be manufactured to current EU GMP standards. Where IMPs and NIMPs are required for use within a clinical trial, the first choice is generally to use a medicine with a UK Marketing Authorisation. Alternatively, a medicine with Marketing Authorisation in another EU member state can be used. Medicines can be specifically manufactured for use in a clinical trial and sometimes this may be the most cost-effective or practical option, but the final IMP must still comply with current EU GMP standards. It is important to remember that the requirement to meet GMP applies both to the medicine under investigation and also to any placebo or comparator compounds. Establishing the licensing status of any IMPs/NIMPs and potential manufacturing steps at an early stage will inform the MHRA CTA submission and processes which may need to be in place to demonstrate that the medicine was of sufficient quality and under appropriate control. This can be a complex area particularly when import of an IMP is undertaken from a third country e.g. The USA. Guidance on the exact requirements is available in Eudralex Volume 10.

As with other elements in a clinical trial, it is important that there are formal agreements between the sponsor and a manufacturer responsible for the supply of IMPs. A Technical Agreement is generally used when a sponsor engages a commercial company or NHS production facility to manufacture an IMP for a clinical trial. It outlines the requirements of each party involved; that is the contract acceptor and contract provider. It may cover issues such as audit, responsibility for recall, provision of supporting documentation and dealing with complaints. Alternatively if medicines are to be provided free of charge from a commercial company, an agreement will normally be set up between the parties again outlining the responsibilities of each party. These documents are crucial as they dictate the responsibilities, timelines, and provision of medicines and pharmacy staff can have a significant input to the development of such agreements in conjunction with R&D staff.

MHRA CTA Submission
Preparing the MHRA CTA submission is often a key milestone in the set-up of the study. Pharmacy staff again can have key role in ensuring that the submission is completed correctly and efficiently. Guidance is available on the submission requirements. A short explanation of some of the key pharmaceutical documentation that needs to accompany the submission is provided below.

Investigator's Brochure (IB) - this provides information and evidence to explain the rationale for the proposed clinical trial and the safe use of the IMP in the trial. An investigator's brochure will generally follow a set format.

The approved SmPC can be used in place of an IB if the IMP is authorised in any EU member state and is used according to the terms of the Marketing Authorisation. When the IMP is used out with the license then the SmPC should be complemented with a summary of relevant non-clinical and clinical data to support the use of the IMP in the clinical trial in the proposed study protocol.

IMPD - an IMPD must be provided for novel IMPs unless a sponsor has previously been granted a clinical trial authorisation by the competent authority in which case they can refer back to the earlier submission. It is also possible to refer to an IMPD submitted by another sponsor for the same product. An IMPD is also required if an IMP is manufactured from an Active Pharmaceutical Ingredient (API). Example: An IMPD would be required for a contract manufacturer producing a levothyroxine containing capsule using an API as a starting material. An IMPD is a complex and document which requires expert input of the manufacturer. It includes information on excipients, manufacturing processes, conformance to TSE requirements, product specifications and batch analysis. Further guidance on the content of an IMPD is available.
A simplified IMPD (sIMPD) may be submitted if the information relating to the IMP has been assessed previously for example as part of a marketing authorisation in any member state of the EU. Example: A sIMPD would be required for a contract manufacturer producing a levothyroxine containing capsule by over-encapsulating a medicine with an EU Marketing Authorisation. Information on a placebo may also be provided as a simplified IMPD. An NIMP dossier may also be required as part of the submission.

**Labelling** - pharmacy involvement is crucial in labelling to ensure that the final information that appears on the IMP labels is clear and fit for purpose. The legislation does allow IMPs to be supplied without specific clinical trial labelling when the IMP is being used in accordance with the Marketing Authorisation but justification for the absence of labelling still needs to be included in the CTA submission. Labelling requirements are provided in Annex 13 to Good Manufacturing Practice.

**Manufacturer’s Authorisation** - only manufacturers that are specifically licensed by the relevant EU Competent Authorities may manufacture medicines or placebos for use in a clinical trial. The Manufacturer’s Authorisation is required for each site where manufacturing activities will occur.

**Ethical considerations**
Whilst the Ethics Committee is specifically tasked with ensuring that a clinical trial meets the required ethical standards, all those involved in the review and development of a clinical trial have an obligation to ensure that the rights and well-being of the patient are inherently protected by the study processes. Clinical trial pharmacists can provide valuable input into the patient information sheet, particularly on the sections on the use of IMPs and NIMPs, possible alternatives for treatment, possible benefits, disadvantages and risks of taking part as well as what happens when research stops/availability of medicines at the end of the study.

**Financial**
For non-commercial research, pharmacy staff can again provide valuable information on potential costs that may be incurred as a result of the clinical trial. The following list is an example of potential costs:

- IMP and NIMP cost or API
- IMP/NIMP manufacturing, assembly and storage
- Costs incurred as part of audit
- Other manufacturer related costs eg. sample storage quality control analytical checks, stability testing work, maintenance of recall and or shipment tracking facilities
- Qualified Person’s release for IMPs imported from third countries
- Distribution costs – dependent on stability information and storage requirements
- Dispensing fees charged by pharmacy sites particularly if it is a multi-site clinical trial or involves complex dispensing
- Any extra equipment that will be required to be purchased by pharmacy in order to accommodate any safety issues associated with preparation, storage, handling or use of IMP and/or comparators eg. -80°C freezer
- Preparation of randomisation schedules and statistical advice
- Development and use of IVRS/IWRS
- Destruction.

**Pharmacovigilance**
The processes of pharmacovigilance reporting for IMPs in clinical trials require that systems are in place to ensure that SAEs, SARS and SUSAR (see Glossary) are rapidly reported to the sponsor once they are reported. Thereafter the sponsor is required to report to the relevant Competent Authority, the Eudravigilance database and ethics committee as appropriate. The IB or SmPC will normally includes information on
the expected adverse reactions including the frequency and it is this information against which SUSARs are assessed and pharmacy may be asked to assist in pharmacovigilance related decisions or in the preparation of Development Safety Update Reports (DSUR). Guidance on pharmacovigilance for clinical trials is available.

**Pharmacy site set-up and training**

Under Good Clinical Practice, the expectation is that staff involved in the study will be trained in the study processes. In non-commercial clinical trials, a pharmacy manual is often developed in order to provide written information on expected standards and as a basis for training. It stands to reason that pharmacy staff are ideally placed to develop pharmacy training manuals and supporting documentation.

Pharmacy staff can also give advice on ‘assembly’ of IMPs which is permitted without the requirement to hold a MA IMP. Manufacture includes any process carried out in the course of making the product but does not include dissolving or dispersing the product in, or diluting it or mixing it with, some other substance used as a vehicle for the purposes of administering it. No person is permitted to manufacture or assemble an IMP unless they hold the correct Manufacturing Authorisation or meet what is often termed the ‘section 37 exemption.’ This specific exemption in the regulations permits the assembly of IMPs to be conducted in hospitals or health centres by a doctor, pharmacist or person under the supervision of a pharmacist provided it is assembled exclusively for use in the hospital or health centre or at another hospital or health centre that is a trial site for the same clinical trial.

To assemble an investigational medicinal product is defined as:

(a) Enclosing the product (with or without other medicinal products of the same description) in a container which is labelled before the product is sold or supplied, or used in a clinical trial, or

(b) Where the product (with or without other medicinal products of the same description) is already contained in the container in which it is to be sold or supplied, or used in a clinical trial, labelling the container before the product is sold or supplied, or used in a clinical trial, in that container.

Pharmacy can also have an ongoing role in assisting in resolution of issues highlighted through monitoring of pharmacy sites and ongoing update of processes and procedures in relation to the investigational medicinal product.
3.3 Pharmacy Review of a Clinical Trial Protocol

Objectives:
- To be aware of the different aspects of a pharmacy protocol review before commencing a trial
- To have an understanding of the process of reviewing a trial protocol.

Any trial hosted in a UK site must have regulatory and ethics approval in place before it can commence. The application for these approvals is done via the Integrated Research Application System (IRAS) – a single system allowing information to be submitted once for perusal by all relevant authorities and bodies before granting approval.

Thereafter, before a trial can be hosted in any NHS centre, approval must be granted by the local Research and Development (R&D) department. Information is submitted to R&D in the form of a Site-Specific Information (SSI) form. The form lists all local professional groups/services who will be involved in the trial, for example, pharmacy, laboratory and radiology staff. Each group must indicate to R&D that they are in support of the trial before R&D will formally ‘sign off’ to approve hosting of the trial in the NHS centre. Support is usually indicated by the relevant personnel signing the SSI form although a copy of an email indicating support may be attached to the original form. Additionally, especially for commercial trials or for trials where suggested treatment is significantly different to the current standard care it may be advisable to forward a report detailing extra workload and any foreseen additional costs to R&D.

The target timeline for SSI approval set by the Scottish Government is 30 days. Pharmacy review is a small part of this approval process and the expected turnaround for pharmacy review of a trial protocol is usually no longer than 10 working days.

The process is broken down into a number of stages which will be carried out by a Clinical Trials Pharmacist and/or Pharmacy Technician. The stages ensure that a trial is comprehensively reviewed to take into account any regulatory, clinical, technical & financial aspects before a trial is given pharmacy approval (see Figure 4).

Figure 4
Pharmacy Review of a Clinical Trial Protocol
3.3.1 Regulatory Review

The Pharmacist must check regulatory approvals are in place before pharmacy approval is given namely:

- MHRA Approval (in the form of Clinical Trial Authorisation [CTA])
- Ethics Committee Approval.

The pharmacist must check that the approvals relate to the latest version of the protocol and that there are no significant amendments pending.

Copies of the approvals will be required for filing in the pharmacy trial file and electronic copies are usually obtained either from the local R&D department or from the clinical trial co-ordinator listed in the protocol.

3.3.2 Clinical Review

This phase of the protocol review would often be completed by a Pharmacist.

The pharmacist would review the following information:

**Trial design**

- Commercial or Non Commercial
- Phase of trial
- Medication identified as Investigational Medicinal Products (IMPs)
- Randomisation options (open label/blinded/placebo controlled?)
  - For randomised trials, how is randomisation done?
    - Paper envelope system/IWRS or other system?
    - Who carries out the randomisation – what is the extent of pharmacy involvement in this stage?
  - Who has responsibility for code break of the randomisation if required?
    - Will any code break procedure (e.g. sealed envelopes) be held by pharmacy?
    - Can pharmacy support this both during working hours and out of hours?
- Duration of trial.

**Patient group**

- Diagnosis/indication being investigated
- Is the trial clinically appropriate?
  - If possible, compare with any current treatment guidelines/formularies or other information
- Expected accrual of patients in treatment centre
- Treatment location – as inpatient or outpatient?

**Clinically relevant information for the IMP(s)**

- Is the IMP/comparator being used for a licensed indication?
  - If licensed check against SmPC information that the drug and dose is appropriate for the indication?
  - If unlicensed, request copy of the Investigator Brochure (IB) for any IMP from the sponsor/Contract Research Organisation (CRO) to confirm that proposed doses are supported by information in the IB
- Any known contraindications, side effects or interactions?
- Any information on administration of the IMP?
  - Route of administration, frequency and duration of treatment
  - Any specialised information/counselling required for the trial subject?
  - Any specialised training required for staff administering?
- Any specific monitoring requirements e.g.
  - Cumulative doses
  - Blood tests
  - Fluid balance
- Any other medicines being given as non investigational medicinal products (NIMPs) or for supportive care?

**Trial prescription**

- Will the sponsor provide a trial specific prescription? /can in house paperwork be used?
• Can the local pharmacy suggest amendments to the prescription form if it is not suitable for local use?

Prior to or during the time period of the formal pharmacy review of a clinical trial, the reviewing pharmacist may participate in a multi-disciplinary team (MDT) meeting to discuss feasibility of running the trial. This may be:

• A formal meeting such as a site selection visit (SSV) with a representative from the sponsor/CRO (usually for commercial trials)
• An informal meeting with local colleagues to discuss the trial and to agree whether all affected parties are able to support the hosting of the trial.

Information gleaned from either of these meetings will assist the pharmacist in completing the clinical review.

3.3.3 Financial Review

This phase of the protocol would usually be carried out by the trials pharmacist, supported by a clinical trials pharmacy technician.

Depending on whether the trial is commercial or non-commercial, different financial factors will need to be taken into account.

Commercial studies

• Has the sponsor submitted proposed costings for the trial?
• Are the costings as per the current NIHR (National Institute for Health Research) costings template?
• Do the proposed costings accurately reflect pharmacy workload e.g. the number of dispensing and reconciliation episodes; has the cost of drug storage or destruction been factored in?
• If the costings do not seem to be correct give feedback to local R&D as soon as possible so that they can renegotiate fees.

All studies

• Workload associated with the study:
  - What additional workload will the trial attract for pharmacy staff?
  - How often will the trial be monitored?
  - Can pharmacy support the trial with the current staffing structure?
• Provision of IMP
  - Is the Investigational Medicinal Product free of charge or supplied by the sponsor?
  - If the IMP is not provided, will the cost of procuring it for the trial be greater than the standard associated with current standard care of the clinical indication in question. If so, additional costs should be indicated to R&D in the course of providing pharmacy approval for the trial.
• Trial exit strategy
  - Will treatment be complete for patients once trial treatment is finished?
  - If not:
    ▪ Will the sponsor continue to supply the IMP in an open label study or for compassionate use?
    ▪ Will the local health board become liable for provision of the medicine? What approval processes would the medicine have to go through before it can be prescribed? What are the cost implications?
• Any other potential additional costs?
  - e.g. to destroy returned IMP; to provide designated IMP storage space, especially if the IMP must be stored in a fridge; archiving requirements.
3.3.4 Technical review
This phase of the protocol would usually be carried out by the trials pharmacist, supported by a clinical trials pharmacy technician.

Sourcing Clinical Trial Investigational Medicinal Products (IMPs)

- Is the IMP commercially available (manufactured by a company with a UK/EU manufacturing authorisation (MA)) or provided as a trial specific IMP?

- For trial specific IMPs
  - Is the IMP manufactured as per Good Manufacturing Practice (GMP)?
    - All IMPs must be manufactured in the UK/EU or a country with whom the EU has a Mutual Recognition Agreement (MRA) to assure that GMP processes have been followed.
    - As per GMP all manufacturers must have finished products released by a Qualified Person (QP). Relevant copies of QP release certificates and manufacturing certificates of analysis must be able to be presented to local centres either with any IMP delivery or upon request.

- For IMPs manufactured outwith the UK/EU, if the country does not have an MRA in place, IMPs must be imported and re-released by a company with a manufacturing authorisation, under the authority of a QP.

- Does the sponsor specify any unusual ordering procedures? e.g. via IWRS or using trial specific paperwork when placing orders.

Availability of product information

- Is the formulation appropriate to the patient group?
- For licensed products, is there a SmPC available?
- For unlicensed products, is there an Investigator Brochure (IB) available?

- Any specific COSHH data available?
- Does the sponsor provide a pharmacy manual with any other IMP-specific information?

Receipt of IMP(s)

- Any specific instruction from the sponsor about procedures to follow when the IMP is received?
  - Should the stock be over-labelled upon receipt?
  - If the IMP is provided with a ‘temp trace’ device are there specific instructions for extracting temperature data?
    - In particular: does the local health board/IT department support the insertion of USB temp trace devices into local computers?

- For trial specific IMPs, if appropriate, will QP release certificates or certificates of analysis be sent with every shipment or must they be requested separately?

Storage of IMP(s)

- What is the storage location? – room temperature/fridge or freezer
- Does the sponsor specify the exact temperature range for the storage location?
  - Will the sponsor provide their own calibrated thermometer(s)?
  - Any specific advice from the sponsor about dealing with temperature excursions?
- Any other storage requirements e.g. protect from light?
- How much IMP will be supplied?
  - What size will the containers be?
  - Is there sufficient space to store the IMP, especially if fridge storage is required?
**Labelling of IMP(s)**
- For trial specific IMPs, will they be supplied with Annex 13 compliant labelling?
  - Reviewing pharmacist may need to request a sample of the IMP labels from the sponsor
- For non-trial specific IMPs, will the sponsor provide supplementary Annex 13 compliant labels or will they be produced in house?

**Dispensing IMP(s)**
- Any specific details in the study about how to dispense the IMP?
  - Does the trial require aseptic dispensing?
  - Should it be dispensed in original packs?
  - Are there detachable labels which must be retained in the pharmacy file?
  - Will the sponsor supply trial specific accountability logs or should they be designed in house?

**Handling returns**
- What should happen to partially used vials/returned IMP/empty containers?
- Does the sponsor require that all returned/partially used IMP is quarantined for monitoring purposes?
- Does pharmacy have space to store all returns?

**Destruction of IMP(s)**
- Can unused/returned IMP be destroyed locally?
  - Is it sufficient to seal returned stock in a cin bin for destruction off site or must the stock be incinerated on site?
  - Does the sponsor provide trial specific paperwork to document IMP destruction?
- Does the sponsor require a copy of any in house standard operating procedure (SOP) for drug destruction?

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**3.4 Setting Up a Hosted Clinical Trial**

*This section outlines the pharmacy aspects of setting up a clinical trial.*

**Objectives:**
- To understand the role of pharmacy staff in setting up a clinical trial
- To describe the necessary components of a pharmacy clinical trial file.

Local set up of a hosted clinical trial usually only commences once regulatory and ethical approvals are in place. The application for these approvals is done via the Integrated Research Application System (IRAS) – a single system allowing information to be submitted once for perusal by all relevant authorities and bodies before granting approval.

Thereafter the stages involved in setting up a hosted clinical trial, with the personnel involved at each stage, are as detailed below:

![Trial Set-Up Process (Pharmacy)](image_url)
Site selection visit (SSV)
This only occurs for some commercial trials when the sponsor or delegated Contract Research Organisation (CRO) visits a local site to meet with relevant personnel, view premises and to discuss the feasibility of a trial being hosted at the site. The sponsor/CRO will then provide feedback to the site in the form of a Site Selection Visit Report which indicates whether the sponsor/CRO wishes to pursue hosting the trial at that site.

SSI (Site Specific Information) form
The SSI form is submitted by local Principal Investigator (PI) or their delegate to Research and Development (R&D) to request local approval to host the trial in an NHS site. All parties affected by the running of the trial e.g. pharmacy, laboratories, radiology must sign the SSI form to indicate that they have reviewed the protocol and give agreement and local support for hosting the trial. This process must be completed within 30 days (as per the standard set by the Scottish Government).

Pharmacy review of the protocol (as part of the SSI approval process)
This is a lengthy process involving several different aspects:

- Regulatory, clinical, technical & financial review of the protocol is undertaken by the Clinical Trials Pharmacist and Pharmacy Technician
- For commercial trials the proposed costs have to be agreed with R&D for incorporation into the contract to be signed with the sponsor
- For non-commercial trials it is important to indicate any additional costs associated with the trial to R&D so any effect on budget is noted.

See the previous section for specific details of what comprises the pharmacy review.

R&D approval given
This stage involves the completion and signing of Clinical Trial Agreement (the formal contract between R&D and the sponsor) to agree terms, conditions and respective responsibilities for hosting the trial.

Review of pharmacy standard operating procedures (SOPs)
At this stage the Clinical Trials Pharmacist and Pharmacy Technician need to ensure Clinical Trial Standard Operating Procedures (SOPs) are in place for all sections where clinical trial work will be undertaken e.g. Dispensing and Final Release of study drugs, Drug Accountability, Storage and Safe Handling of study drugs, Emergency Code Break, Preparation of Pharmacy Instructions etc. SOPs should be regularly reviewed and controlled by clinical trials Pharmacy Staff.
Setting up Pharmacy Trial File

The pharmacy clinical trial file should be prepared by the pharmacy technician and approved by the Clinical Trials Pharmacist. All appropriate documentation should be included within the file. It is advisable to check with the sponsor regarding whether a pharmacy file will be provided before starting to set up an in house version.

Typically a pharmacy file should comprise:

- Index
- Prescribers signature log
- Trial name/Eudract No.
- Internal pharmacy delegation log (PDL)²
- Sponsor details
- Patient registration log
- Contact information
- Storage instructions
- Monitoring log
- Medicine information³
- Pharmacy instructions (SOPs)
- Copy of the protocol
- Sample prescription forms/worksheets
- Regulatory documentation⁴
- Supplementary dispensing labels
- Financial agreement
- Drug Accountability logs¹
- Payment request log

Table 4
Contents of the Pharmacy Clinical Trial File

If a section of the folder is left empty a file note should be inserted, explaining this.

Preparation of Pharmacy Instructions

The pharmacy instructions should be prepared by the pharmacy technician and approved by the Clinical Trials Pharmacist. These should include any instructions pharmacy personnel require to dispense the IMP including preparation of worksheets and design of accountability logs if appropriate. Details of how to order further CTIMP supplies and how to manage returns/destruction of CTIMPs is usually also included.

Site Initiation Visit

A trial cannot commence at an NHS site before the sponsor has formally ‘initiated’ the site. The initiation may take place remotely via tele- or video-conference or in person with the trial co-ordinator visiting the site. The meeting should be attended by all relevant healthcare personnel including the Principal Investigator at the site, Research Nurse, Data Manager, laboratory/radiology staff, Clinical Trials Pharmacist and Pharmacy Technician.

During Site Initiation formal checks are carried out to ensure the site is ready to start running the trial, including a recap of trial design, eligibility criteria, data collection requirements, SAE (serious adverse event) reporting and ensuring the site delegation log has been completed.

Ordering/Receipt of CTIMPs

Ordering and receipt of the CTIMP is the role of the pharmacy technician or Clinical Trials Pharmacist. Supply of the CTIMP to a site may be initiated by the trial co-ordinator or it may need to be ordered by pharmacy staff.

Trial specific CTIMPs should be stored in a designated separate area apart from all other stock at all times. Record receipt of the stock in the trial master accountability log.

¹ Drug accountability logs: master logs and subject-specific logs
² PDL records the signatures of all pharmacy personnel who will work within the trial
³ Medicine information includes the SPC, Investigator Brochure (IB) and COSHH information
⁴ Regulatory documentation: MHRA, MREC, R&D, management approval
Pharmacy Staff Training
Training of all appropriate pharmacy staff should be delivered by the Clinical Trials Pharmacist or pharmacy technician. It is important to ensure that any training required is documented and all staff members sign the Pharmacy Delegation Log in the Trial File once it has been completed.

Trial is ‘live’
As patients are recruited and prescriptions sent to pharmacy for dispensing the CTiMP is supplied to trial subjects according to trial procedures and in-house standard operating procedures. This role may be performed by the Clinical Trials Pharmacist and pharmacy technician or it may be delegated to non-clinical trials pharmacy staff who have been appropriately trained.

Ongoing internal review/external monitoring
The clinical trial process should be regularly internally reviewed to provide ongoing quality assurance of all in house processes. This monitoring is the responsibility of the Clinical Trials Pharmacist or pharmacy technician. Furthermore, the trial will undergo external monitoring at time periods specified by the sponsor.
chapter 4

Monitoring, Management and Inspections
This chapter looks at what is expected of pharmacy staff involved in commercial and non-commercial trials. The process of inspections for clinical trials and the role of pharmacy staff within them are also covered.

Objectives:

- To understand the pharmacist’s role in clinical trial management
- To understand need for detailed documentation of all aspects of a trial
- To be aware of the differences between commercial and non-commercial trials
- To understand the different types of inspection for clinical trials and the role of pharmacy staff in them.

What Monitors/Clinical Research Associates (CRAs) expect from Pharmacy

Clinical Trials can be commercial or non-commercial, drug or non-drug based. Only drug based clinical trials will involve pharmacy. These are known as clinical trials of investigational medicinal product (CTIMPs).

Commercial Trials

The monitoring of commercial clinical trials within hospitals is carried out by Clinical Research Associates (CRAs) or Monitors working on behalf of the sponsor.

The CRA will visit the site prior to the study starting to ‘initiate the study’ and ensure that all relevant documentation is in place. The monitor will visit the pharmacy department to ensure that pharmacy staff involved in the study are aware of their responsibilities. The monitor will then revisit the pharmacy at regular intervals to ensure that all relevant details are being recorded as specified within the trial protocol.

The monitor will check the pharmacy file to ensure that:

- Data is complete, accurate and verifiable from source documents
- There is adherence to the protocol/SOP and GCP
- All required documentation is present and complete
- All correspondence is being filed appropriately
- Medication is being stored correctly
- All medication is accounted for and in date
- Site Identification and Delegation Log is up-to-date and complete
- All staff involved in the trial are on the Delegation Log or the Site Training Log.

This will include any electronic information sent or received as part of the trial. Subject Identification Logs will be reviewed to ensure that as subjects enter the study their details are being recorded.

In commercially run studies, responsibility for continuation of supply rests with the monitor or supply may be handled by automated services. Supply of all items required for the trial should be checked by the monitor as part of their routine visit. At each pharmacy visit the Site Visit Log should be signed by the monitor and countersigned by a member of the pharmacy clinical team.

Pharmacies performing Clinical Trials are expected to:

- Have suitable storage facilities
- Have SOPs and any other relevant documentation in place and available
- Have suitably trained staff
- Receipt medication
- Dispense medication
- Complete medicine accountability & reconciliation.
Storage Facilities
Demonstration of packaging or package dimensions of the IMP by the sponsor or CRA in advance of or at initiation is important to ensure that sufficient and appropriate storage space is made available before receipt of product.

Adequate space is required for storage of:
- Usable product
- Quarantined product
- Product returned by patient.

IMP is required to be kept within the correct environmental conditions (e.g. 2-8°C or below 25°C) and therefore calibrated temperature monitoring devices are required and daily logs of temperature recorded. Any temperature deviations outwith the defined ranges must be reported to the CRA/sponsor, the IMP quarantined and the process of resolving it must be documented.

SOPs/Documentation
As part of the overall quality system within an organisation, it is expected that all pharmacies have SOPs and any relevant documentation in place before the trial starts. There is no specific requirement that this is checked by the sponsor during site evaluation, although this could be inferred from the sponsor’s responsibility to select investigators with adequate resources (ICH GCP 5.6.1). Many sponsors or CRAs will ask for copies of these SOPs in advance of initiation of the study.

Training
Documented training of pharmacy staff in study specific IMP handling before starting the study is required. This must be documented within the pharmacy site file. All core pharmacy staff named on the delegation log for the study must have up-to-date GCP training.

A one-page CV for all core pharmacy staff involved in the clinical trial needs to be available as part of the study documentation. This should indicate their experience, training (e.g. GCP) and qualifications to facilitate the study.

Core staff should be trained by the CRA for each individual trial, the trained staff should then cascade the training to other relevant staff and all training should be documented within a training log kept in the trial folder.

Trial Identification and Delegation Logs identify key tasks delegated by the principal investigator. Doctors, nurses and core pharmacy staff involved in a trial should be named on this document.

Pharmacy study specific training records should note the names of all pharmacy staff who have received in house training and by which core clinical team member.

Receipt of IMP
The receiving process for an IMP ensures that the medication is available and of appropriate quality before it is used within the study.

Receipt of IMPS should be carried out as described in the protocol- usually adapted to meet local procedures. Often this is by phone (interactive voice receipt system -IVRS) or via a web site (interactive web receipt system -IWRS). Damaged items and defects in the product must be reported at this stage.

Some protocols require pharmacy to have a ‘QP Batch release certificate’ for the received medication; this should be available before the receipt process is fully completed. IMP without a QP batch release certificate (or statement of the quality of the product from the sponsor) available must be kept in quarantine and not used until it is available.
Dispensing
Only those named in the Identification and Delegation Logs and with the appropriate key tasks are able to prescribe IMPs for patients involved in a study.

All dispensing and labelling activities should be completed by following individual trial protocols and SOPs and carried out by staff identified on the training logs.

Medicine Accountability & Reconciliation
All IMPs received and supplied must be documented and accounted for. This is often completed through the IVRS/IWRS and a series of paper documentation. All medication supplied to patients is accounted for via dispensing logs; any medication returned by patients is reconciled with the amount dispensed vs. the amount expected to be consumed, as per the dosing schedule.

Non Commercial (Academic) Trials
Where the clinical trial is non-commercial in nature, monitoring is the responsibility of the sponsor organisation and they are unlikely to send CRAs. A Non-Commercial Sponsor may delegate some monitoring activity to the sites via remote monitoring processes elsewhere, e.g. completion of a questionnaire. Generally, the extent and nature of monitoring will depend on the complexity of the trial.

For non-commercial trials the pharmacy department is often responsible for ensuring that there are sufficient medication supplies and again is expected to:

- Have suitable storage facilities
- Have SOPs and any other relevant documentation in place and available
- Have suitably trained staff
- Receipt medication
- Dispense medication
- Complete medicine accountability & reconciliation.

The Inspection Process
The MHRA's Good Clinical Practice (GCP) Inspectorate is part of the Inspections & Standards Division of the MHRA. Their responsibility is to assess the compliance of any organisations that are conducting clinical trials using investigational medicinal products with the UK and EU legislation. Statutory Instrument 2004/1031 and subsequent amendment 2006/1928 provide the legal basis for these inspections.

The organisations that could be inspected by the MHRA include pharmaceutical companies, contract research organisations, non-commercial organisations such as universities, NHS Trusts and charities, investigational trial sites, clinical laboratories, GCP archives and other facilities involved in clinical trial research.

Since 2009, the MHRA have adopted a risk-adapted approach to their inspection process. This means that they take consideration of the scope, frequency and depth of inspections depending on how the organisation involved takes responsibility for their compliance with the regulations. The MHRA assess an organisation's control of their risk by gathering a combination of information from a variety of sources (the Compliance Report, internal information about previous inspection history, organisational changes and other compliance reports). From this information an organisation will be categorised as high, medium and low risk and inspections are prioritised for those with the highest risk category. A small proportion of organisations from the medium or low risk categories are also randomly selected for inspection.

Organisations engaged in clinical trials with IMP will be requested to complete a Compliance Report once every two years. This details the number of clinical trials that an organisation is involved in along with the numbers of patients recruited and the types of products under investigation.
Once the risk assessment has been determined and an inspection scheduled, the organisation to be inspected will be contacted and requested to complete a GCP Inspection Dossier. This contains the detailed information about how the organisation operates and is used by the MHRA to prepare for the inspection. The inspection will conclude with a closing meeting where any findings by the MHRA will be verbally reported to the organisation.

Types of inspection

There are three types of Good Clinical Practice (GCP) Inspections:
- Routine inspections
- Triggered inspections
- Requested.

Routine inspections

Routine Inspections are carried out to assure compliance with the relevant legislation within commercial and non-commercial organisations and these will be notified in advance.

When chosen for inspection the organisation will receive notification and a request for information including:
- A list of clinical trials
- Organisational charts
- Standard operating procedure (SOP) lists and selected SOPs
- Key contact details
- An overview of facilities.

This information is used to allocate resources, create an inspection plan and set the inspection fee. The inspection plan is developed with the organisation to ensure that all activities are covered and that appropriate personnel are available for interview. A number of clinical trials are normally selected for detailed Trial Master File (TMF) review, although the inspection may not be limited to these.

During the inspection, all requested documentation should be provided for review and relevant staff should be available for interview.

Findings and reporting of routine inspections

Any deficiencies found during a routine inspection are classified as ‘Critical’, ‘Major’ and ‘Other’ findings. The inspectors may also make some observations and recommendations within the report.

Critical: there is evidence that significant and unjustified departure(s) from applicable legislative requirements have occurred that may affect the safety of participants or the integrity of the data collected, or a number of ‘Major’ findings have accumulated and not been resolved. Critical findings are routinely referred to the MHRA’s Clinical Trial Inspection Action Group (CTIAG).

Major: a non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a ‘critical’ issue, but may have the potential to do so unless addressed and/or there is evidence of the failure of quality systems.

Other: there is evidence that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.

Further information can be found in the references at the end (MHRA GCP document).

Triggered inspections

These inspections are carried out to answer specific questions raised or to satisfy the MHRA that a specific trial has been conducted in accordance with legislation relating to the conduct of clinical trials. For example a trial sponsor may trigger an inspection of a site hosting their study, if they
have concerns about practices there. The relevant organisation may not always be notified of these inspections in advance and planning may not be shared.

**Requested Inspections**

The Committee for Medicinal Products for Human Use (CHMP) can request GCP inspections in relation to marketing applications made using the EU centralised procedure. The European Medicines Agency (EMEA) coordinates these inspections, which are conducted by inspectors from the EU Member States.

**Pharmacy Role in Inspections**

When an organisation has received notice of a routine site inspection of a hosted clinical trial, the pharmacy staff involved should carry out a check of the pharmacy files that will be inspected. Ideally pharmacy files should be maintained in a state of audit-readiness at all times and the check should involve ensuring that all documents are stored as listed within the File Index as supplied by the sponsor. All documentation listed should be filed and up-to-date, with notes of superseded versions. Any gaps in the documentation should be accounted for with reasons, if they are not being kept.

Pharmacy staff should be prepared to be interviewed during any inspection of a clinical trial. This will involve discussions of their procedures and staff should ensure that their SOPs and training files are available for examination.

An NHS organisation may also be inspected in their role as a sponsor and/ or host of clinical trials. Depending on local arrangements, pharmacy services may be much more involved in the IMP management processes of their locally sponsored studies and may hold QP batch release documentation and other quality related information on behalf of the organisation. They may also have been involved in the development of study specific procedures for the use of the IMP and labelling etc. A local task force or equivalent led by the R&D department is often set-up in order to prepare for inspection and pharmacy staff should be involved in preparing for inspection as an integral part of the sponsor team. The R&D Forum website has information on preparing for inspection but there are limited resources available on the internet to assist pharmacy in preparing for an MHRA inspection.
chapter 5

Pharmacy and the Research Team
This chapter describes the main role of the various bodies and individuals involved in clinical trials in Scotland and explains when pharmacy staff may be involved with each party in the course of their clinical trials work.

Objectives:

- To be aware of the national and local bodies involved in co-ordinating, supporting and regulating clinical trials
- To be aware of the key personnel involved and their roles in conducting a clinical trial
- To be aware of the key issues relating to pharmacovigilance and monitoring of clinical trials.

NHS Research Scotland

NHS Research Scotland (NRS) is an initiative between the Chief Scientist’s Office (CSO) and the NHS Health Boards in Scotland to ensure that NHS Scotland provides the best environment to support clinical research. The NHS Boards are organised, by geographical location into 4 nodes: NRS North (NHS Grampian and Highland), NRS East (NHS Tayside, Fife and Forth Valley), NRS South East (NHS Lothian) and NRS West (NHS Greater Glasgow and Clyde, Ayrshire and Arran, Dumfries and Galloway, Golden Jubilee and Lanarkshire). The Health Boards and the CSO work together to support both commercial and non-commercial patient orientated research. They work together to develop common, simplified systems and mechanisms to achieve this aim and make NHS Scotland an attractive location to perform research.

The NRS Strategy Group provides oversight of the operation of NRS and is made up of the CSO and the Research and Development (R&D) directors from the four lead health boards within the nodes (NHS Grampian, Tayside, Lothian and Greater Glasgow and Clyde). The efficiencies achieved through the NRS assist in the delivery of the CSO research strategy. The NRS provides the NRS Permissions Co-ordinating Centre which provides a streamlined approach to gaining necessary approvals for research within Health Boards.

Research Networks

There are 7 research networks represented within the NRS research nodes each promoting collaborative working within a different clinical area. The Scottish Research Networks include Cancer, Stroke, Dementia, Diabetes, Mental Health, Medicines for Children and Primary Care. The Scottish Cancer Research Network is split geographically matching the Regional Cancer Networks SCRN North (NoSCAN: NHS Tayside, Grampian, Highland, Western Isles, Orkney and Shetland), SCRN South East (SCAN: NHS Lothian and Borders), and SCRN West (WoSCAN: NHS Greater Glasgow and Clyde, Forth Valley, Ayrshire and Arran, Dumfries and Galloway and Lanarkshire). Each of the nodes has a network lead and these individuals will co-ordinate the research across the node within the research network speciality. This will involve co-ordination with the research staff within each of the contributing networks to ensure that patient accrual statistics are maintained and maximised.

Pharmacy staff may encounter representatives of the research network during the initiation of new studies within the network and have ongoing contact throughout the life of the study. Where the studies involve Investigational Medicinal Products (IMPs) pharmacy will be involved in the appropriate ordering, receipt, storage and issuing of the IMPs and the maintenance of accountability records.

Ethics/National Research Ethics Service (NRES)

Prior to gaining approval for the study the Chief Investigator/Sponsor must seek ethical approval for the study through submitting the required documentation for the study to a Research Ethics Committee. This process has been simplified through the use of the Integrated Research Application System (IRAS). This keeps the former structure of the National Research Ethics Service and uses filters to complete the required forms.
ensuring that only the forms applicable for the type of research study are completed. This will then permit submission for ethics approval to a specific Research Ethics Committee (REC) or to the REC which will convene soonest.

Pharmacy staff will be required to ensure that when trials are initiated that the appropriate copies of the ethical approvals are included in the site file (whether the main site file or the Pharmacy Site File). Pharmacy staff will also be required to ensure that the documentation to support any amendments and the corresponding ethical approvals are also filed in the site file.

**Research and Development (R&D)**

When any study has received a favourable ethical opinion from an appropriate Research Ethics Committee and has then received appropriate authorisation from the Medicines and Healthcare Regulatory Agency (MHRA), local approval from the participating health board R&D department is required prior to commencing the study. This may involve the confirmation that all staff and departments involved in the delivery of the study have been involved and given their approval for the study, ensuring that the appropriate financial approvals are in place and that the clinical trials agreement has been appropriately signed by the Health Board or their designee. This will ensure all the necessary approvals and agreements are in place.

Pharmacy staff may come into contact with the R&D department to ensure that local pharmacy approval is in place for the study. In addition following an amendment to the study or protocol, R&D will be required to confirm that they have accepted the amendment and may contact pharmacy to ensure that there are no problems with the amendment. R&D departments will also be involved in managing the funds obtained from the CSO.

**Clinical Trials Unit**

The Clinical Trials Unit (CTU) will be involved in the operation and design of clinical studies. This may be a local CTU or a co-ordinating CTU depending on the study involved. The CTU will be associated with the Research Nodes and take a lead role in the clinical research performed within the research networks. For multicentre studies it is common for a co-ordinating CTU to be managing the study – particularly in the case of non-commercial studies. The CTU will usually be attached to an academic unit which may oversee the majority of the management of the study on behalf of the sponsor and perform some of the responsibilities of the sponsor.

**Clinical Research Facility**

The main purpose of the clinical research facility (CRF) is to facilitate clinical research within the NHS and support the investigators undertaking the research. The support the CRFs provide can range from allowing access to suitable clinical/treatment rooms for patient consultations or for the administration of study medicines, supplying research nurses to perform study assessments, access to statisticians or bio-statisticians or general assistance with study design. CRFs can also play a role in providing training for clinicians involved in clinical trials to ensure that they are appropriately experienced and able to meet regulatory requirements for studies. Where the CRF holds an MHRA Phase I accreditation specialist support is available to help investigators with running or conducting Phase I studies.

Pharmacy staff may encounter a CRF both in terms of supporting the management of IMPs for studies performed within the CRF and in accessing training. There will usually be pharmacy staff associated with the CRF to assist with the pharmaceutical aspect of the clinical trial. CRF pharmacy staff may also have a wider governance role for clinical trials within their respective health boards/research nodes.
Data management centre including validation of electronic data capture

The data management centre will play a role in co-ordinating the information that is recorded during the patient assessment visits during the life of the trial. This information may be captured on paper data capture forms (or case report forms; CRFs) or may be captured using electronic forms (electronic Case Report Forms; eCRFs). The Data Management Centre will be required to clarify any data that is ambiguous or unclear from the forms. The Data Management Centre may send a data query to the site data manager/research nurse to seek clarification regarding the recorded data. This will require examination of the source data e.g. the patient medical records to explain the discrepancy. This is particularly important where the data is collected electronically to ensure that operator error does not lead to the recording of incorrect information.

Pharmacy staff may encounter the Data Management Centre where the data query requires examination of dispensing records or drug accountability records.

Sponsor

The sponsor will be required to fulfil their responsibilities in accordance with the Medicines for Human Use (Clinical Trials) Regulations particularly relating to the aspects of the trial related to the use of IMPS and the reporting of adverse events. The sponsor must have made appropriate pharmacovigilance arrangements to satisfy their responsibilities. The Sponsor, or their designee, must comply with the requirements for reporting SAEs and SUSARs to the regulatory authority (MHRA) in accordance with the clinical trials authorisation. The sponsor is responsible for ensuring that all issues related to the study are resolved. This may also involve the submission of the appropriate documentation to obtain ethical and regulatory approval for the study. Pharmacy staff may be involved with the project manager where the pharmacy has a role to play in the procurement or manufacture of IMPS and their subsequent management.

Project Manager

The project manager may be involved in the initial design of the trial and be required to work with the Chief Investigator and the Sponsor to ensure that all issues related to the study are resolved. This may involve the submission of the appropriate documentation to obtain ethical and regulatory approval for the study. The Project manager may also be required to liaise with individual departments to ensure that the respective departments are able to deliver the study design within the agreed timescale. This may involve arrangements with the IMP manufacturer and ensuring that the appropriate documentation is provided to support the release of the IMP in accordance with regulatory requirements.

Pharmacy staff may be involved with the project manager where the pharmacy has a role to play in the procurement or manufacture of IMPS and their subsequent management.

Principal Investigator

The principal investigator is the lead clinician who is responsible for the operation of the trial on a single site in accordance with Good Clinical Practice and Medicines for Human Use (Clinical Trials) Regulations. The investigator is also responsible for ensuring that all staff involved in the clinical trial are qualified by knowledge and experience and must ensure arrangements are in place to cover the operation of the trial and provide for participants in the trial. The sponsor will also appoint a Chief Investigator for the study.

Pharmacy staff may encounter the sponsor through routine communication of study amendments, drug safety reports, and monitoring of trial activities on participating sites. In some cases pharmacy staff may be required to perform self-monitoring activities in accordance with the study requirements. Pharmacy staff will need to meet sponsor requirements in relation to IMP management including ordering, receipt, accountability, destruction and temperature monitoring.
that staff detailed on the site delegation log are competent to carry out their duties. The investigator therefore has overall responsibility for how the clinical research is carried out on the site. The investigator must also ensure that they are suitably qualified to carry out the research in accordance with ethical and regulatory responsibilities. The Principal Investigator is also responsible for communicating with the Chief Investigator for multi-site trials.

Pharmacy staff will be in contact with the Principal Investigator on a day-to-day basis throughout the life of the trial (or the co-investigators or their designees) ensuring that any CTIMP trials are appropriately prescribed in accordance with the trial requirements. The Principal Investigator and Pharmacy will also be responsible for the reporting of any Serious Adverse Events (SAE) or Suspected Unexpected Serious Adverse Reactions (SUSARs) in accordance with the trial requirements to the Sponsor or their designee. Pharmacy staff may also be required to assist with un-blinding of study treatment at the request of the Principal Investigator or the Chief Investigator, in accordance with the study requirements.

Research Nurse
The research nurse will be a key member of the site research team for the individual clinical trial. The research nurse may be involved in managing a portfolio of trials or may be involved in individual trials. The nurse must be qualified by knowledge and experience both in the field of research and in the clinical speciality. The nurse will be involved in the day to day operation of the trial and may undertake consenting of patients for the trial on behalf of the Investigator. The trial nurse may also be responsible for the collection and handling of clinical blood samples and for the completion of data collection forms for patients. The nurse will also be required to maintain the Case Report Forms and Patient Files for the study.

Pharmacy staff may be involved on a day-to-day basis with the research nurse especially when the study is a Clinical Trial of Investigational Medicinal Products (CTIMPs), with pharmacy ensuring that the prescribed medicine is appropriately prescribed by the investigator and ensuring that the accountability records are appropriately maintained in accordance with the requirements of the trial.

Pharmacovigilance
Where studies involve CTIMPs there must be a mechanism for reporting adverse reactions to study drugs or adverse events related to the trial. Where a causal relationship is suspected with the study medication this must be reported. In some studies this may be to the sponsor or their designee, and this may involve the pharmacovigilance department. The reports will be examined and where there is a risk to study participants the reactions/events will be reported to the MHRA and be included in Annual Safety Reports. Where the reactions are unexpected and serious i.e. a SUSAR the events must be reported to the MHRA in an expedited manner and communication circulated to the participating centres. In some cases this may precipitate an amendment to the study.

Pharmacy staff may be involved in contacting the pharmacovigilance team to assist the research nurse or Principal Investigator in reporting SAEs, SARs, or SUSARs in accordance with the trial requirements. Pharmacy staff will also be a point of contact should it be determined that a study drug is recalled in response to issues identified by the sponsor or the pharmacovigilance team.

MHRA as regulator
The Medicines and Healthcare Products Regulatory Agency (MHRA) is the regulatory body which issues authorisations for clinical trials. This agency ensures that the Medicines for Human Use (Clinical Trials) Regulations are adhered to during the operation of clinical trials. Amendments to the clinical trial must also be submitted for approval. The MHRA must be informed of any SAEs, SARs, and SUSARs in accordance with the regulations. The MHRA may also inspect any clinical trial and may send MHRA GCP inspectors to investigate clinical trials.
Pharmacy staff may encounter the MHRA in response to submitted SAEs, SARs or SUSARs or drug safety reports. In addition pharmacy may receive amendments which have been approved by the MHRA via the sponsor or their designee.

**Governance/Monitoring**
Each study that is performed must be carried out in accordance with GCP and the Clinical Trials Regulations. Each Health Board will therefore have Standard Operating Procedures (SOPs) and Operations Manuals to support the delivery of clinical trials. This may be overseen by the R&D Director or similar individual within the organisation. The SOPs and Operations Manual will form part of a quality management system detailing the responsibilities of individuals involved in clinical research. This will fit within the organisational Clinical Governance Framework and Risk Management Framework ensuring that all clinical trials activities are carried out in accordance with applicable legislation. The clinical research activities should be subject to both internal and external monitoring to ensure compliance with regulatory and legislative requirements. The trial sponsor may engage the services of a Clinical Research Organisation (CRO) to perform monitoring of trial activities on participating sites. The CRO would then highlight areas of non-compliance and the site staff would agree corrective actions. These reports and responses would then be submitted to the Study Sponsor. It may also be appropriate for the internal audit department to assist with this process to ensure compliance with existing NHS guidance.

**IMP Manufacturer**
Where the trial involves an IMP this must be manufactured by a manufacturer with an appropriate licence/authorisation for this activity. The manufacturer must be able to confirm that the product has been manufactured in accordance with Annex 13 of Good Manufacturing Practice and that it meets the correct product specification and has been released by a Qualified Person (QP Release). In addition it must be labelled in accordance with Annex 13 and with labels approved for the trial. The sponsor must be able to confirm that if the IMP Manufacturer is from a third world country that the appropriate authorisations are in place.

Pharmacy staff will encounter the IMP manufacturer in terms of assessing that the IMP manufacturer satisfies the appropriate requirements in accordance with applicable legislation. The pharmacy assessment of the clinical trial should ensure that the sponsor has supplied the relevant documentation and that there is sufficient confidence in the manufacture and supply of IMP from the sponsor.

**Patient**
The patient will give informed consent to participate in the trial, and once consented will be randomised within the trial (where the trial is randomised in design). Pharmacy staff may encounter the patient where IMPs are dispensed for the patient during the study and may be required to determine that the patient’s prescribed treatment is appropriate in accordance with the study protocol. Pharmacy staff may also be required to provide patient education regarding the study or collect additional information regarding the patient treatment depending on the requirements of the study. Pharmacy may be involved in the assessment of patients receiving treatment and assist in the completion of CRFs.

**Independent Data Monitoring Committee**
An independent data-monitoring committee (IDMC) is one that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Pharmacy staff may encounter the IDMC where a decision is made to make an amendment to the trial as an outcome of the review of data. Pharmacy staff may also encounter the IDMC where a decision is made to terminate a study early.
**Trial Steering Committee**

The trials steering committee (TSC) will provide overall supervision for a trial on behalf of the Trial Sponsor and the Trial Funder. While day-to-day management of the trial is the responsibility of the investigators, the Chief Investigator may wish to set up a Trial Management Group (TMG) to assist with this function. The TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question. The TSC will provide advice, through its Chair, to the Chief Investigator, the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial.

Pharmacy staff may encounter the TSC through communications from the Sponsor or the Chief Investigator where new information has been considered or on occasions where it is suspected that a breach in adherence to the protocol has been suspected or confirmed.

**Trial Management Committee**

The trial management committee (TMC) will normally include the individuals responsible for the day-to-day management of the trial such as the chief investigator, statistician, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. Pharmacy may encounter the TMC when the day to day operation of the trial is being examined, particularly where non-adherence is suspected or reported.

**Other allied professions e.g. imaging**

Other allied professions may be required to participate in the trial through the provision of support services e.g. radiology imaging. There may be a specific requirement regarding the type of imaging required and the method of reporting e.g. to RECIST criteria. Pharmacy staff may be required to liaise with other allied professions to ensure that the appropriate study requirements are met.
chapter 6

Clinical Trials IT Systems
This chapter describes some important developments in the information technology systems used in clinical trials and when they might be used.

Objectives:

- To be aware of important developments in clinical trials IT systems
- To be aware of the main advantages and disadvantages of the systems in use.

Electronic Case Report Form (eCRF)
The development of electronic Case Report Forms (eCRFs) has allowed data to be collected during a study which is less, or not, dependent on paper-based systems. In most cases data collection using eCRFs reduces the need for storage space, while allowing faster collection of data. The use of eCRFs also means that data collection exhibits fewer discrepancies through the use of in-built edit checks and allows on-line randomisation. The introduction of eCRFs has also highlighted issues related to Trust Firewalls and slow connections. The presence of paper CRFs are not dependent on availability of internet connection, and as no password protection is necessary it allows completion of CRF's during staff shortages.

The use of eCRFs will increase and this may ease issues related to the secure storage of paper-based records and provide improved efficiency as missing data is easily highlighted. This could impact on pharmacy as the technology could be extended to electronic accountability and dispensing records.

Interactive Voice /Web-based Response Systems (IVRS/ IWRS)
The development of Interactive Voice Response Systems (IVRS) and Interactive Web-based Response Systems (IWRS) have changed how clinical trials operate. These systems allow certain activities to be automated using the telephone or internet. This can be applied to randomisation and particularly IMP receipt. These systems require the user to use an identification number or code to record the receipt of IMP by the Pharmacy. In some cases this system can also be used to trigger IMP supply. This allows a limited number of individuals to be able to access the system giving better governance, but this also means that care has to be taken to ensure that trained staff will always be available to complete these tasks during periods of absence.

Electronic patient diary
The increasing use of mobile phone or tablet computer technology has allowed the use of electronic patient diaries to support the recording of patient data during clinical trials. Patients are supplied with a mobile phone or other mobile computing device which has the capability of sending patients responses to questionnaires to a central data collection location. This has the benefit of allowing daily monitoring for example in relation to side-effects of treatment or tolerability of treatment. It also allows real-time collection of data rather than retrospective using paper questionnaires during assessment visits.
chapter 7

Other Pharmacy Issues
This chapter outlines some of the issues surrounding documentation and information storage.

Objectives:
- To be aware of the factors influencing the methods of record keeping for clinical trials
- To be aware of the main considerations to ensure all documentation is carefully made and stored.

Archiving
The method of archiving should be considered carefully with regard to clinical trials given the potential volume of documentation required and the length of time that the data should be archived in accordance with the trial requirements. Where archiving is carried out on-site the space available and the cataloguing system should be robust enough to ensure that all the required information is available in the same location and can be retrieved to assist in re-construction of the trial at a later date. It may be necessary to access source documentation, for example patient medical records, and there must be a robust system in place to ensure that the source documentation is also retained for the time required by the trial.

Where archiving is contracted to an outside agent this must comply with the relevant legislation, for example Data Protection Act etc. The retention of records and the differing requirements with regard to destruction should be highlighted within the contracted service. Consideration should be given to archiving all the documentation associated with the trial in the same location.

Information Security
Where clinical trials data is stored electronically this must be secured in accordance with the relevant information security guidance within the NHS. The data must be retrievable and consideration must be given to ensuring that the records will be maintained for the life of the trial in accordance with the trial requirements. Advice may have to be sought from IT departments regarding the practicality of ensuring that information is appropriately backed-up and retained securely.

Good documentation Practices
All staff should be aware of good documentation practices and there should be SOPs describing best practice. All data should be recorded in a consistent manner with alterations made without obscuring the previous entry(ies). Dates must be recorded in a standard format which reduces the potential for alteration for example 27 Jun 2012. Any alterations must be properly recorded with single lines being put through previous entries and no correction fluid being used. Any discrepancies must be recorded using File Notes where necessary.
## Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AcoRD</td>
<td>Attributing the cost of health and social care Research &amp; Development</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ARSAC</td>
<td>Administration of Radioactive Substances Advisory Committee</td>
</tr>
<tr>
<td>ATMP</td>
<td>Advanced Therapy Medicinal Product</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>COSHH</td>
<td>Control of Substances Hazardous to Health</td>
</tr>
<tr>
<td>CPAS</td>
<td>Chemotherapy and Pharmacy Advisory Service</td>
</tr>
<tr>
<td>CRF</td>
<td>Clinical Research Facility (or Case Report Form)</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical (or Contract) Research Organisation</td>
</tr>
<tr>
<td>CSO</td>
<td>Chief Scientific Officer</td>
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<tr>
<td>CRA</td>
<td>Clinical Research Associates</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
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<tr>
<td>CTIAG</td>
<td>Clinical Trial Inspection Action Group</td>
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<tr>
<td>CTIMP</td>
<td>Clinical Trial of Investigational Medicinal Product</td>
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<tr>
<td>CTU</td>
<td>Clinical Trials Unit</td>
</tr>
<tr>
<td>(e)CRF</td>
<td>(electronic) Case Report Form</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Reports</td>
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<tr>
<td>EMA (EMEA)</td>
<td>European Medicines Agency</td>
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<tr>
<td>GAfREC</td>
<td>Governance Arrangements for Research Ethics Committees</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GTAC</td>
<td>Gene Therapy Advisory Committee</td>
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<tr>
<td>IB</td>
<td>Investigational Brochure</td>
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<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>IMPD</td>
<td>Investigational Medicinal Product Dossier</td>
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<tr>
<td>IRAS</td>
<td>Integrated Research Application System</td>
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<tr>
<td>IVRS</td>
<td>Interactive Voice Response Systems</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web-based Response Systems</td>
</tr>
<tr>
<td>MA</td>
<td>Marketing Authorisation</td>
</tr>
<tr>
<td>mCTA</td>
<td>Model Clinical Trial Arrangements</td>
</tr>
<tr>
<td>MDT</td>
<td>Multi-Disciplinary Team</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare Regulatory Authority</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MREC</td>
<td>Medical Research Ethics Committee</td>
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<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
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<tr>
<td>NIMP</td>
<td>Non-investigational Medicinal Product</td>
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<tr>
<td>NPSA</td>
<td>National Patient Safety Agency</td>
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<tr>
<td>NRES</td>
<td>National Ethics Research Service</td>
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<tr>
<td>NRS</td>
<td>NHS Research Scotland</td>
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<tr>
<td>PDL</td>
<td>Pharmacy Delegation Log</td>
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<tr>
<td>PIS</td>
<td>Participant Information Sheet</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>QP</td>
<td>Qualified Person</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SCRN</td>
<td>Scottish Cancer Research Network</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Medicinal Product Characteristics</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SReDA</td>
<td>Scottish Research Database Application</td>
</tr>
<tr>
<td>SSI</td>
<td>Site Specific Information</td>
</tr>
<tr>
<td>SSV</td>
<td>Site Selection Visit</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMC</td>
<td>Trial Management Committee</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Group</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathies</td>
</tr>
<tr>
<td>VHP</td>
<td>Voluntary Harmonisation Procedure</td>
</tr>
</tbody>
</table>
References

**General**

www.ClinicalTrials.gov
www.MHRA.gov.uk

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*Principles of Clinical Research* Edited by Ignazio Di Giovanna and Gareth Hayes. Wrightson Biomedical Publishing Ltd 2001

*Trial by Fire: Lessons from the History of Clinical Trials*, Allan Gaw

**Regulatory**

Good Manufacturing Practice (Eudralex Volume 4)
Good Manufacturing Practice (MHRA)
Good Manufacturing Practice: Annex 13 Investigational Medicinal Products
Good Clinical Practice (ICH E6)

Detailed guidelines on good clinical practice specific to advanced therapy medicinal products

Medicines and Healthcare products Regulatory Agency: Clinical trials for medicines

Advanced Therapy Medicinal Products (Human Tissue Authority)
Advanced Therapy Medicinal Products (MHRA)

Clinical Trials for Medicines (MHRA)

Good Clinical Practice (MHRA)

MHRA Good Clinical Practice: Discussion forum and frequently asked questions

**Ethical**

NRES: National Research Ethics Service

Research or Audit (NRES)

Governance Arrangements for research ethics committees (NRES)

Consent and guidelines for patient information sheets (NRES)

Declaration of Helsinki

Health Research Authority

**Pharmacy**

*Advice for pharmacists who need to comply with clinical trials regulations.* The Pharmaceutical Journal 2008; 281: 193-195

National Pharmacy Clinical Trials Network (*Membership is open to members of the Royal Pharmaceutical Society of Great Britain*)

Pharmacy Special Interest Group: Institute of Clinical Research

Chemotherapy and Pharmacy Advisory Service (CPAS)

NIHR CRN Costing Template

British Oncology Pharmacy Association

GCP Pharmacy Resources (NIHR)

**Inspections**


http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Riskbasedinspections/index.htm

www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Theinspectionprocess/index.htm
Organisations supporting research
UK Clinical Research Network Study Portfolio
NIHR: National Institute for Health Research
Medicines Research Council
Health Technology Assessment Programme
Chief Scientist Office (Scotland)
NHS Research Scotland Permissions Coordinating Centre (Scotland)
NIHR CSP (England)

Support for patients participating in research
Healthtalkonline.org: Clinical trials
getrandomised.org
NIHR: Patients and public