NIHR CRN
GCP Resource

A compilation of links to useful on-line GCP quality tools and resources
Acknowledgements

This GCP Resource has been produced by Dr Stuart McCully of Compliance Healthcheck Consulting UK Ltd (www.chcuk.co.uk) on behalf on the National Institute of Health Research (NIHR)
DISCLAIMER

Although this GCP Resource contains information of a legal nature, it has been developed for information and education purposes only and does not constitute legal advice or opinions as to the current operative laws, regulations, or guidelines of any jurisdiction. In addition, because new standards are issued on a continuing basis, this GCP Resource is not an exhaustive source of all current applicable laws, regulations, and guidelines relating to non-interventional studies. While reasonable efforts have been made to assure the accuracy and completeness of the information provided, researchers and other individuals should check with the applicable National Competent Authorities and/or Research Ethics Committees before starting research activities.

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Foreword

The following document contains links to GCP-related articles, references, documents and websites and is aimed to serve as a resource to help develop and further your knowledge about Good Clinical Practice (GCP). For further details, or to add anything to this document, please contact the CRN Workforce Development team:

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<tr>
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<td>1. <strong>Updated all Hyperlinks</strong> – All of the hyperlinks within the document have been updated to capture recent updates to various websites (e.g., MHRA, NIHR, Department of Health, ICH etc)</td>
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<td>2. <strong>New Sections Added</strong> – The resources document has been expanded to capture the whole of the clinical trial process from ignition through to completion and archiving. As a result the following new sections have been added</td>
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<tr>
<td>a. Good Clinical Practice: Recent Changes</td>
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<td>3. <strong>Expanded Section: Study Set Up: Responsibilities, Approvals and Essential Documents</strong> – This section has been expanded to include the following elements with a view to supporting sponsors of clinical trials:</td>
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<td>a. Clinical Trial Insurance</td>
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<tr>
<td>4. <strong>Addition of Common Inspection Findings</strong> – The relevant sections have been updated to include examples of common inspection findings</td>
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Good Clinical Practice – Recent Changes

The section aims to highlight recent changes in the legislation, standards and guidelines that are applicable to the conduct of clinical research in the UK. The reader should be aware that this is just a ‘snap shot’ of recent GCP-related changes that may have an impact on your daily practice.

The section captures the following updates:

- Changes to legislation
- Changes to procedures
- Guidance and discussion papers – Future Direction

Changes to Legislation

Clinical Trials Directive (2001/20/EC) (Beyond 2012)

- Revision of the Clinical Trials Directive (Implementation expected after 2012)

  On 9 February 2011, the European Commission published a consultation paper on a “concept paper on the revision of the 'Clinical Trials Directive' 2001/20/EC” for public consultation

  The European Commission is planning to put forward, in 2012, a legislative proposal to revise the Clinical Trials Directive 2001/20/EC

  Resources:

  European Commission Website: Clinical Trials

  European Commission Website: Clinical Trials – Major Developments

  European Commission Concept Paper on the Revision of the 'Clinical Trials Directive' 2001/20/EC

Mandatory Electronic SUSAR Reporting (Sept 2010)

- SUSARs originating in the UK must be reported via the MHRAs eSUSAR website from 1st Sept 2010

  MHRA Guidance
eSUSAR website

Updated Pharmacovigilance Requirements (July 2012)

The Pharmacovigilance requirements for marketed drugs which are set forth in Directive 2001/83/EC have been updated via Directive 2010/84/EC. These requirements must be transposed into UK law by 21st July 2012.

One of the major changes (in accordance with Article 104.2) is that the marketing authorisation holder will be required to keep a note of the major PV audit findings in their pharmacovigilance system master file until such times as these findings have been addressed:

“The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.”

Summary:

- Directive 2010/84/EC (to be transposed into UK law by 21st July 2012)

  **Audit Reports**: Note of main audit findings to be placed in the pharmacovigilance system master file until the corrective actions have been fully implemented.

  **Adverse Reactions**: Definition updated

  **Post-Authorisation Studies**: Greater clarity on requirements for post-authorisation safety and efficacy studies

Regulation of Pharmacists, Pharmacy Technicians & Pharmacy Premises (Feb 2010)

From 27th September 2010, the General Pharmaceutical Council (GPhC) will regulate pharmacists, pharmacy technicians and registered pharmacy premises

- Legislation
  - The Pharmacy Order 2010 (SI 2010/231)

- The General Pharmaceutical Council (GPhC)
From 27 September 2010, the GPhC will regulate pharmacists, pharmacy technicians and registered pharmacy premises.

It is the GPhC’s job to protect, promote and maintain the health, safety and wellbeing of patients and of those who use pharmaceutical services.

The GPhC was established after the government decided the Royal Pharmaceutical Society of Great Britain (RPSGB) could no longer be both a regulator and a leadership body.

The establishment of the GPhC brings the pharmacy profession into line with all other healthcare professions, which are regulated by independent regulators.

Resources:

- The General Pharmaceutical Council (GPhC)
- Royal Pharmaceutical Society of Great Britain (RPSGB)

**Advanced Therapy Medicinal Products (ATMPs) (Aug 2010)**

What is an advanced therapy medicinal product (ATMP)?

The following definitions are taken directly from Regulation EC/1394/2007 and are provided in case the reader wants examples of these types of products.

a) Advanced therapy medicinal product’ means any of the following medicinal products for human use:

   a. A gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

   b. A somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

   c. A tissue engineered product as defined in point (b).

b) ‘Tissue engineered product’ means a product that:

   a. contains or consists of engineered cells or tissues, and

   b. is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
A tissue-engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

c) Cells or tissues shall be considered ‘engineered’ if they fulfil at least one of the following conditions:

a. The cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

b. The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

b) ‘Combined advanced therapy medicinal product’ means an advanced therapy medicinal product that fulfils the following conditions:

a. It must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and

b. Its cellular or tissue part must contain viable cells or tissues, or

c. Its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

• Legislation

Regulation EC/1394/2007 (in force from 30th Dec 2008)


• Resources
Medical Devices (March 2010)

- Legislation (Latest update - March 2010 through SI 2008/2396)

Currently four sets of Medical Device Regulations implementing all of the Medical Devices Directives and amendments to date

**SI 2002/618** (Consolidated legislation),

**SI 2003/1697** (Amendments to cover the re-classification of breast implants and additional requirements covering devices utilising materials from TSE susceptible animal species),

**SI 2007/400** (Amendment to cover the re-classification of total hip, knee and shoulder joints)


- Resources

MHRA Website: Medical Devices

NIHR Website: Medtech Study Start-up Route Map

NIHR GCP Resource: Medical Devices, the Law and Good Clinical Practice

Changes to Procedures

MHRA GCP Inspection Process (Oct 2009)

The GCP risk-based inspection process was launched in May 2009 and was implemented from October 2009. It uses a combination of information provided to the MHRA on the Compliance Report, internal information about previous inspection history, organisational changes and other compliance reports with the results of intelligence gathering to determine an organisation’s control of their risk.
The resulting risk assessments will be categorised into high, medium and low risk and inspections prioritised for the companies with the highest risk category. For internal control purpose, a small proportion of organisations from the medium and low-risk categories will be randomly selected for inspection. Inspections will be scheduled according to how much inspection resource is available in the upcoming year and the results of the Compliance Report used to determine an approximate amount of inspection time required to conduct the inspection.

Completion of the Compliance Report by sponsors, contract research organisation (CROs) or hosting sites is not mandatory. These organisations, however, should be aware that failure to submit a completed Compliance Report will result in being assigned to a high-risk category. Currently, phase 1 units, clinical laboratories and individual investigators not acting as sponsors of clinical trials are not required to complete a Compliance Report.

The results of the risk assessment will be provided to the organisation. If there are any concerns regarding the risk assessment this should be sent to the GCP risk-based inspection mailbox (gcpriskbasedinspections@mhra.gsi.gov.uk).

- Risk Based Inspections

  The scope, frequency and depth of inspections is now dependent on the company or organisation's compliance risk.

  Now ‘required’ to submit a GCP Compliance Report every year (from May 2009) to be submitted by June of the current year (e.g., June 2011)

- Resources

  MHRA Website: GCP-Risk Based Inspections

  GCP Compliance Report Template

Procedure for Investigating Research Misconduct (July 2009)

The Procedure for the Investigation of Allegations of Misconduct in Research provides researchers’ employers with standards that are thorough and fair to all parties. The standards, prepared by the UK Panel for Research Integrity in Health and Biomedical Sciences, are applicable to all fields of research.

The Department of Health welcomed the publication of the procedures, as it recognises that some high-profile cases have heightened public awareness of poor research practice, affecting public confidence in clinical research. Though rare, when bad research practice
does occur, it can have wide-ranging and damaging consequences. These are made worse if they are not addressed appropriately. The Department of Health is committed to promoting research governance processes that are proportionate to risk and to ensuring that procedures are rationalised.

Research Councils UK advises the adoption of the Procedure in its Policy and Code of Conduct on the Governance of Good Research Conduct.

- The Procedure is a step-by-step manual for investigating allegations of fraud and misconduct in research, applicable to all subject areas and suitable for all organisations engaged in research - Universities, NHS organisations, Private Sector Bodies and Charities.

- Resources:

  UK Research Integrity Office (UKRIO) Website

  UKRIO Procedure for the Investigation of Misconduct in Research (Aug 2008)

  RCUK Policy and Code of Conduct on the Governance of Good Research Conduct: Integrity, Clarity and Good Management (July 2009)

Clinical Research Guidance

Electronic Source Data (Aug 2010)


  Outlines the current opinion of the EU GCP Inspectors Working Group on the use of electronic data capture in clinical trials and on related inspections

  This paper outlines the current expectations of GCP inspectors. Any departure from this paper would need to be justified.

Guideline on Missing Data in Confirmatory Clinical Trials (Jan 2011)

Trial Master File Reference Model (June 2010)

The Document and Records Management SIAC of the Drug Information Association (DIA), a recognized and highly respected professional association, is supporting an initiative to create a Trial Master File (TMF) Reference Model.

Creation of the TMF Reference Model has involved more than 120 representatives, all DIA members, from 90 bio-pharmaceutical companies, contract research organizations (CROs), consultancies, technical vendors, industry groups, healthcare, academia, non-for-profit / NGO and regulatory agencies. Each contributor or stakeholder has provided their perspective on the standardized TMF taxonomy and metadata. The goal of the group was to create the TMF Reference Model, which can be used and adapted by any company. Therefore the attention of participants is drawn to the non-commercial nature of this forum. Although it is acknowledged that the resulting reference model will ultimately need to integrate with commercially available products, this was by no means a forum for promotion of products and companies.

The TMF Reference Model consists of standardized taxonomy and metadata and outlines the clear definition and organization of TMF content using standard nomenclature. The TMF Reference Model output is non-binding in accordance with the DIA’s scope and mission. This model is a reference for the industry and should not be considered mandatory, but rather as an opportunity for standardization across the industry. The TMF Reference Model can be adapted to an electronic or a paper TMF and does not endorse, nor by design, require, any specific technology for application.

Rationale for the creation of a model

The TMF contains those essential documents that individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements (ICH Guideline for Good Clinical Practice, E6, Section 8).

All companies and investigators conducting clinical trials in the pharmaceutical/biotech industry maintain documentation for each clinical trial. Each company has their own unique TMF structure as defined by their SOPs. No comprehensive common model exists for managing TMF documents. Over the conduct of a trial many functions contribute to the TMF, although oversight of the content is usually not one function’s responsibility – resulting in a highly inefficient work processes including but not limited to:

- All drug development companies and CROs expend considerable resources defining the content of the trial master file for each clinical trial. Consequently, Investigators
have the challenge of adapting to different formats and TMF content organization with each clinical trial.

- The burden is very high on smaller companies that usually have limited document management expertise and limited financial resources.
- Records and information exchange between collaborating companies is extremely cumbersome, may prevent the transfer of a drug or joint venture.
- Regulators are challenged with varying terminology and file structures, creating inefficiency and a higher degree of variability during audits.

Regulatory guidance, such as ICH E6 section 8, addresses only a sub-set of TMF documents. Documentation requirements for the set-up and maintenance of quality systems, electronic systems, safety monitoring, and proof of an adequate and well-controlled trial, to name a few, exist in various regulations across many countries or regions, but not in ICH E6. The goal of the TMF Reference Model is to provide a single, unified interpretation of the regulations via document listing, which would be accepted across the industry. It does not provide guidance in the process by which the document is the output.

Summary

- The Drug Information Association (DIA), a recognized and highly respected professional association, is supporting an initiative to create a Trial Master File (TMF) Reference Model.
- Creation of the TMF Reference Model has involved more than 120 representatives, all DIA members, from 90 bio-pharmaceutical companies, contract research organizations (CROs), consultancies, technical vendors, industry groups, healthcare, academia, not-for-profit / NGO and regulatory agencies.
- The goal of the group was to create the TMF Reference Model, which can be used and adapted by any company.
- Resources:
  - DIA Trial Master File Reference Model (June 2010)

Adults Lacking Capacity to Consent (Oct 2010)

NRES has released an on-line toolkit on research involving adults lacking capacity to consent for themselves.
The **toolkit** covers the provisions of the Mental Capacity Act 2005 and the separate provisions for medicinal trials under the Medicines for Human Use (Clinical Trials) Regulations 2004. It includes a specific module on research in emergency medicine.

The **toolkit** is a learning resource for anyone with an interest in understanding the statutory provisions and approval requirements for research, which may include adults lacking capacity at any stage of a project. It will be of particular relevance to researchers designing projects and applying for ethical approval; research managers and sponsors; members of Research Ethics Committees and REC office staff.

The **toolkit** has been designed for NRES by a joint team from the University of Leicester and the University of Bristol, in consultation with a group of stakeholders including researchers, REC members, the NRES policy team and the Social Care Institute of Excellence. NRES wishes to express its appreciation for the work of the design team and the input from stakeholders.

The toolkit is available here ([https://connect.le.ac.uk/alctoolkit/](https://connect.le.ac.uk/alctoolkit/)), together with a set of user instructions on how to make best use of the learning resource. The toolkit requires that your web browser has Adobe Flash installed in order to view it.

All the toolkit materials, together with further guidance about adults lacking capacity and links to other resources including the Mental Capacity Act Code of Practice, are available on our Guidance page under **adults lacking capacity to consent for themselves**.

**Summary**

- **NRES On-line Toolkit**

- An on-line toolkit on research involving adults lacking capacity to consent for themselves. The toolkit covers the provisions of the Mental Capacity Act 2005 and the separate provisions for medicinal trials under the Medicines for Human Use (Clinical Trials) Regulations 2004. It includes a specific module on research in emergency medicine.

**Time to Consent (Sept 2010)**

- How long should potential participants have to consider the invitation to join a research project? ([NRES Discussion Paper](https://connect.le.ac.uk/alctoolkit/), Sept 2010)

**Good Practice in Research and Consent to Research (April 2010)**
• GMC Guidance: Supplementary guidance that sets out the good practice principles that doctors are expected to understand and follow if they are involved in research (Good Practice in Research and Consent to Research – April 2010)

Future Direction of Clinical Research

Equity and Excellence: Liberating the NHS (July 2010)

• The NHS White Paper (Equity and Excellence: Liberating the NHS (July 2010)) sets out the Government's long-term vision for the future of the NHS.

• The vision builds on the core values and principles of the NHS - a comprehensive service, available to all, free at the point of use, based on need, not ability to pay.

• It sets out how we will:

  Put patients at the heart of everything the NHS does;

  Focus on continuously improving those things that really matter to patients - the outcome of their healthcare; and

  Empower and liberate clinicians to innovate, with the freedom to focus on improving healthcare services

• According to the Coalition Governments white paper: ‘Equity and excellence: Liberating the NHS’ (2010):

  • “The government is committed to the promotion and conduct of research as a core NHS role”

  • “Research is vital in providing the new knowledge needed to improve health outcomes and reduce inequalities. Research is even more important when resources are under pressure – it identifies new ways of preventing, diagnosing and treating disease”

  • “The government believes that outcomes will improve most rapidly when clinicians are engaged, and creativity, research participation and professionalism are allowed to flourish”

Academy of Medical Sciences Report (Jan 2011)
• Academy of Medical Sciences Report: A new pathway for the regulation and governance of health research (Jan 2011)

• The Academy of Medical Sciences published its final report
  o (http://www.acmedsci.ac.uk/p118.html)

• The Department of Health (DH) has previously assured on the continued requirement for an efficient and coordinated ethics service and this report adds considerable weight to this statement.

• The Secretary of State for Health, Andrew Lansley said:
  o 'National regulation and local governance of health research are too complex and scattered across too many different bodies. The Academy's report makes the case for simplification under a health research agency that will streamline and co-ordinate regulatory and governance processes. The Government welcomes the report and will consider carefully how to implement its recommendations.'

UK Governments Plan for Growth (March 2011)

This Plan for Growth is an urgent call for action. Britain has lost ground in the world’s economy, and needs to catch up (The Plan for Growth, 2011 - Foreword).

If we do not act now, jobs will be lost, our country will become poorer and we will find it difficult to afford the public services we all want. If we do not wake up to the world around us, our standard of living will fall, not rise (The Plan for Growth, 2011 - Foreword).

In the last decade other nations have worked hard to make their economies more competitive. They have reduced their business tax rates, removed barriers to enterprise, invested in their infrastructure, improved their education systems, reformed welfare and increased their exports (The Plan for Growth, 2011 - Foreword).

Sadly the reverse has happened in Britain over the last ten years. The UK economy stopped saving, investing and exporting and instead turned to a model of growth that failed. It resulted in rising levels of debt, over-leveraged banks, an unsustainable property boom, and a budget deficit that was forecast to be the largest of any of the world’s twenty leading economies. Continuously rising but unaffordable government spending disguised the fact that it was an unsustainable economic boom, with the economy becoming steadily more unbalanced, less competitive and less prepared to meet the challenges of the future (The Plan for Growth, 2011 - Foreword).
We now have to step up a gear. Our economy needs to become much more dynamic, less burdened by pointless barriers, and retooled for a high tech future, if we are going to create the jobs and prosperity we need for the next generation (The Plan for Growth, 2011 - Foreword).

We should never again allow our taxes to become uncompetitive, or drive valued entrepreneurs from our shores. If other nations are turning out smarter school and university students, we have to make sure ours are smarter still. We have to tear down the barriers to enterprise and economic development. Britain should be producing businesses that out-compete, out-smart and out-pace the rest of the world (The Plan for Growth, 2011 - Foreword).

That is what this Plan for Growth is all about. None of it is without controversy – all of it involves choices about our priorities (The Plan for Growth, 2011 - Foreword).

But the alternative is to accept Britain’s economic decline and falling standards of living for our population (The Plan for Growth, 2011 - Foreword).

That is not a future we have to settle for (The Plan for Growth, 2011 - Foreword).

The Plan for Growth: Healthcare and Life Sciences

The NHS and the social care system contributes greatly towards the economy, primarily by increasing health and welfare, which results in greater economic activity that is then reflected in GDP. The NHS is also the largest UK purchaser of products and services from the healthcare and life sciences sectors, and a part of this spending benefits UK based companies and employees. The life sciences sector employs over 100,000 people, largely in highly skilled jobs, in companies ranging from large multi-nationals to SMEs. The sector invests heavily in R&D, accounting for over 28 per cent of all business R&D. The social care market (worth around £24 billion) is a key employment sector in the economy, providing over 1.5 million jobs, 71 per cent of which are providing direct care and support (as per Section 2.179 of The Plan for Growth).

The complexity of health research regulation and governance has increased over the last twenty years through successive legislative changes. National complexity was then compounded by diverse local approval systems, inconsistent, sometimes risk-averse, local interpretations, and confusion about the standards for compliance that apply to different types of research. The Academy of Medical Sciences (AMS) report of its independent review of medical research regulation and governance found that: “UK health research activities are being seriously undermined by an overly complex regulatory and governance environment” (as per Section 2.180 of The Plan for Growth).
The AMS review also called for a full revision of the Clinical Trials Directive (CTD) to ensure that regulatory requirements are proportionate to risk, and to reduce the scope of the CTD by modifying two specific definitions. The AMS report referred to data showing a drop in the UK’s share of global patient recruitment in clinical trials from six per cent in 2000 to two per cent in 2006 (as per Section 2.181 of The Plan for Growth).

Greater collaboration between firms offers opportunities for growth of the sector. The Life Sciences Blueprint, published by the Office for Life Sciences, signalled the beginning of a new approach to supporting translational research collaborations between industry and the public sector by committing to pilot Therapeutic Capability Clusters to capture and promote the UK’s world-leading capability. The clusters work by providing a way for academic institutions, the NHS and industry in life sciences to work together. In October 2010, two pilot clusters were announced (as per Section 2.182 of The Plan for Growth).

Even though there are large numbers of biological science graduates (some 30,000 graduates in 2008-09, almost 10 per cent of all first degree graduates), life sciences employers are reliant on workers from overseas, with a third of the sector’s workforce sourced from abroad. In part, this is due to inadequately skilled UK graduates coupled with shortages in critical areas such as in vivo subjects. Employers have consistently reported that the poor practical and numerical ability of UK bioscience graduates reduces employability (as per Section 2.183 of The Plan for Growth).

The social care sector also suffers from skills shortages. Recruitment vacancy rates are high, just over twice the national average at 3.4 per cent. The turnover rate for care workers in the private sector in 2010 was 24 per cent and 10 per cent in the statutory sector (as per Section 2.184 of The Plan for Growth).

Innovation is a key driver of long-term growth in the sector. There is a long gap between an initial product idea and it reaching the market, and Intellectual Property (IP) protection is critical to ensuring firms ultimately make a return on that investment. At the same time, this protection must not inhibit ongoing innovation (as per Section 2.185 of The Plan for Growth).

Assistive living technologies (often referred to as ‘telecare’ and ‘telehealth’) enable health and social care services to be provided remotely, for example by monitoring vital health signs and using sensors to detect movement or falls. The main barriers are the lack of properly evaluated evidence, the high cost per unit and low levels of awareness of the benefits this technology can bring. As the findings from the Department for Health’s Whole System Demonstrator programme (the largest randomised control trial of this technology in the world) begin to emerge this year, it will deliver a clear evidence base to help move this forward (as per Section 2.186 of The Plan for Growth).
In social care, micro-enterprises can face regulatory barriers to entering the market and fall within regulations which were never intended to affect social care providers. For example, private hire vehicle licensing can capture social care workers transporting those receiving social care. This sort of regulatory barrier can prevent new providers entering the market (as per Section 2.187 of The Plan for Growth).

The UK’s strengths in healthcare and life sciences also have significant export potential. By supporting the development of NHS intellectual property, the Government could help the sector better leverage its brand in overseas markets (as per Section 2.188 of The Plan for Growth).

Summary of Healthcare and Life Sciences Review actions (refer to pages 91 to 98 of the “Plan for Growth”):

1. The Government will set up a new health research regulatory agency to streamline regulation and improve the cost effectiveness of clinical trials. It will make future National Institute for Health Research (NIHR) funding to providers of NHS services conditional on meeting benchmarks, including a 70 day benchmark to recruit first patients for trials.

2. The Government will reduce perceived gold-plating and increase the proportionality of EU Clinical Trials Directive (CTD) and its application.

3. The Government will open up information about clinical trials to enable the public to get involved.

4. The Government will build a consensus on using e-health record data to create a unique position for the UK in health research.

5. The Government will open up information on clinical research to promote collaboration and innovation.

6. The Government will consider opening up prescribing data.

7. The Government will form new Translational Research Partnerships from its £775 million investment in NIHR Biomedical Research Centres and Units.

8. The Government will remove any barriers that limit the further development of geographical clusters, working with industry, local government, universities, NHS and funders.

9. The Government will launch a competition to form a Cell Therapy Technology and Innovation Centre.
10. To ensure educators provide the skilled individuals the sector needs to grow, the Government will, through Cogent, improve market signalling by bringing companies and educators together.

11. The Government will ensure that the Intellectual Property (IP) system supports life sciences businesses.

12. The Government will take forward a range of measures to encourage innovation in NHS procurement.

13. The NHS Chief Executive will provide a report by November 2011, in consultation with industry, academia and other interested parties, on how the adoption and diffusion of innovations can be accelerated across the NHS. This report will inform the strategic approach to innovation in the reformed NHS.

14. The Government will take forward a package of measures to improve the take up of assisted living technology.

15. The Government will strip out regulations that were never meant for the social care market and are preventing market entry and flexible services.

16. The Government will establish a proactive, entrepreneurial NHS Global to make the most of the NHS brand internationally and to offer support and advice to NHS trusts.
The Role of the NIHR CRN in Clinical Research

Clinical research is, and has always been, at the very heart of the NHS. Only by carrying out research into "what works" can we continually improve treatment for patients, and understand how to focus NHS resources where they will be most effective (NIHR CRN CC – About Us).

The National Institute for Health Research (NIHR)

In 2006, the Department of Health set up the National Institute for Health Research to create a world-class health system within the NHS, with the Clinical Research Network as part of this wider organization (NIHR CRN CC – About Us).

At the centre of what we do is the Portfolio – a collection of high-quality clinical studies that benefit from the infrastructure provided by the Clinical Research Network. Many of these studies are Randomized Controlled Trials - considered by many in the medical profession to be the most robust form of clinical trial - although we also support other types of well-designed research (NIHR CRN CC – About Us).

This is how, in practice, we provide an "infrastructure" to support our Portfolio studies:

- We run the coordinated system for gaining NHS permission (CSP) - a system through which researchers can apply for permission to run a clinical study in the NHS. We are constantly working to speed up and simplify this process, so that researchers can get a clinical study up and running quickly, with the minimum of bureaucracy.

- We fund research support posts in the NHS, and provide training, so that researchers have access to experienced "front-line" staff, who can carry out the additional practical activities required by their study such as obtaining patient consent for participation, carrying out extra tests, and collecting the clinical data required for the research.

- We provide funding to meet the costs of using facilities such as scanners and x-rays that are needed in the course of the study, so that research activity adds value to patient care, and doesn't drain NHS resources.

- And we provide practical help in identifying and recruiting patients onto Portfolio studies, so that researchers can be confident of completing the study on time, and on target.
The Clinical Research Network (CRN)

Although the Clinical Research Network operates as one organisation, we are made up of a number of different parts:

- Six “Topic” Research Networks (covering Cancer, Dementia and Neurodegenerative Diseases, Diabetes, Medicines for Children, Mental Health and Stroke)
- A Primary Care Research Network to support research in this part of the health service
- A Comprehensive Clinical Research Network, which covers all other disease areas.

The Clinical Research Network Coordinating Centre (CRN CC)

The final element of the Clinical Research Network is the Coordinating Centre, which is responsible for managing the overall performance of the Networks. In addition to this, the Coordinating Centre team develops and delivers streamlined central systems (CSP), and undertakes specialist cross-cutting activities to support the commercial life-sciences industry, develop the research workforce, and promote patient and public involvement in clinical trials (NIHR CRN CC – About Us).

Key points to consider:

- NHS Researchers work as part of a bigger NIHR family that includes the clinical research network that provides infrastructure support to achieve the national agenda to increase clinical research activity
- All NHS Researchers have an important part to play in the delivery of a national plan for clinical research
- The national plan is highlighted in the NHS Operating Framework (2009/10) that outlines the requirement for all NHS organisations to engage in clinical research activity. This is further supported by the 2011/12 NHS Operating Framework, which re-asserts that the promotion and conduct of research is a core NHS function.
- The validity of patient centred care is outlined in the NHS Constitution Document (2010). Patients and the public have an important role to play and are increasingly looking for opportunities to be involved
The coalition government is committed to promoting the role of clinical research within the NHS:

- As outlined in the white paper: *Equity and Excellence – Liberating the NHS (2010)*
- As supported in the coalition governments 2011 “Plan for Growth”

- *The NIHR Delivery Plan: Embedding Health Research 2009/10* is a valuable document on the role of clinical research in the UK today

### Key Documents Outlining the Role of Clinical Research in the NHS

- **Equity and Excellence – Liberating the NHS (2010)**
  - “The government is committed to the promotion and conduct of research as a core NHS role”
  - “Research is vital in providing the new knowledge needed to improve health outcomes and reduce inequalities. Research is even more important when resources are under pressure – it identifies new ways of preventing, diagnosing and treating disease”
  - “The government believes that outcomes will improve most rapidly when clinicians are engaged, and creativity, research participation and professionalism are allowed to flourish”

- **NHS Operating Framework (2011/12):** The Operating Framework for the NHS in England 2011/12
  - The White Paper, Equity and excellence: Liberating the NHS was published on 12 July 2010 and outlines the Government’s plans for a new direction for the NHS. The Department of Health have already started an ambitious programme of reforms in the NHS with the Revision to the Operating Framework for the NHS in England 2010/11, published on 21 June 2010. This *Operating Framework for the NHS in England 2011/12* sets out the challenges in implementing the first full year of the transition. 2011/12 is a critical period that requires all parts of the health service to respond positively to the principles and purposes set out in Equity and excellence: Liberating the NHS, whilst ensuring service quality and financial performance are maintained and improved.
The promotion and conduct of research is a core NHS function. Continued research and the use of research evidence in design and delivery of services is key to achieving improvements in outcomes. The NHS Life Sciences Delivery Board affords the NHS the opportunity to work with the life sciences industries and roll out best practice so that it can deliver the financial savings that are being driven by QIPP. For example, the Board’s remit to increase access to cost effective innovative medicines and medical technologies will be pivotal to improving quality and realising savings as the NHS evolves into its new structure (as per Section 3.9 of the NHS Operating Framework (2011/12))

- **NHS Constitution for England (2010)**
  - The NHS aspires to the highest standards of excellence and professionalism – in the provision of high-quality care that is safe, effective and focused on patient experience; in the planning and delivery of the clinical and other services it provides; in the people it employs and the education, training and development they receive; in the leadership and management of its organisations; and through its commitment to innovation and to the promotion and conduct of research to improve the current and future health and care of the population (As per Section 1.3 on page 3 of the NHS Constitution (2010))

- **The Plan for Growth (March 2011):** The Coalition Governments Plan for Growth (March 2011)

  - Summary of Healthcare and Life Sciences Review actions (refer to pages 91 to 98 of the “Plan for Growth”):
    - The Government will set up a new health research regulatory agency to streamline regulation and improve the cost effectiveness of clinical trials. It will make future National Institute for Health Research (NIHR) funding to providers of NHS services conditional on meeting benchmarks, including a 70 day benchmark to recruit first patients for trials.
    - The Government will reduce perceived gold-plating and increase the proportionality of EU Clinical Trials Directive (CTD) and its application.
    - The Government will open up information about clinical trials to enable the public to get involved.
The Government will build a consensus on using e-health record data to create a unique position for the UK in health research.

The Government will open up information on clinical research to promote collaboration and innovation.

The Government will consider opening up prescribing data.

The Government will form new Translational Research Partnerships from its £775 million investment in NIHR Biomedical Research Centres and Units.

The Government will remove any barriers that limit the further development of geographical clusters, working with industry, local government, universities, NHS and funders.

The Government will launch a competition to form a Cell Therapy Technology and Innovation Centre.

To ensure educators provide the skilled individuals the sector needs to grow, the Government will, through Cogent, improve market signalling by bringing companies and educators together.

The Government will ensure that the Intellectual Property (IP) system supports life sciences businesses.

The Government will take forward a range of measures to encourage innovation in NHS procurement.

The NHS Chief Executive will provide a report by November 2011, in consultation with industry, academia and other interested parties, on how the adoption and diffusion of innovations can be accelerated across the NHS. This report will inform the strategic approach to innovation in the reformed NHS.

The Government will take forward a package of measures to improve the take up of assisted living technology.

The Government will strip out regulations that were never meant for the social care market and are preventing market entry and flexible services.

The Government will establish a proactive, entrepreneurial NHS Global to make the most of the NHS brand internationally and to offer support and advice to NHS trusts.
• **Best Research for Best Health (2006):** Best Research for Best Health: A New National Health Research Strategy, January 2006
  
  o “Best Research for Best Health: A New National Health Research Strategy” was launched in January 2006 with the aim of making the UK ‘the best place in the world for health research, development and education’
  
  o The mission is to create a health research system in which the NHS supports outstanding individuals, working in world class facilities, conducting leading edge research, focused on the needs of patients and the public
  
  o The vision is to improve the health and wealth of the nation through research.

• **NIHR CRN CC:** National Institute for Health Research Clinical Research Network Coordinating Centre
  
  o The National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) supports clinical research and helps to facilitate the conduct of trials and other well-designed studies within the NHS.
  
  o **Research Networks:** The NIHR CRN CC is working to develop and strengthen NHS infrastructure to support the delivery of clinical research. This is being achieved through the work of Clinical Research Networks, which coordinate and support research in all areas of disease and clinical need.
  
  o **Clinical Research:** As well as supporting the creation of additional research infrastructure, the NIHR CRN CC is working with key partners to improve the clinical research environment as a whole. This includes: developing a high quality Clinical Research Portfolio, offering a regulatory and governance advice service, supporting the work of Clinical Trials Units, working closely with funders.

  
  o The Research Governance Framework outlines principles of good governance that apply to all research within the remit of the Secretary of State for Health. Research governance is one of the core standards for health care organisations (As per paragraph 1 of the Foreword).
  
  o Sets out a framework for the governance of research in health and social care. The framework applies to all research that relates to the
responsibilities of the Secretary of State for Health. That is, research concerned with the protection and promotion of public health, research undertaken in or by the Department of Health, its non-Departmental Public Bodies and the NHS, and research undertaken by or within social care agencies. It includes clinical and nonclinical research; research undertaken by NHS or social care staff using the resources of health and social care organisations; and any research undertaken by industry, charities, research councils and universities within the health and social care systems that might have an impact on the quality of those services (As per paragraph 1.2 of Section 1.0)

**NIHR Quality Tools & Templates**

**Investigator Site File Contents**

- Investigator Site File Contents
  - Divides the Investigator Site File into sections for ease of use and reference.
  - Refer also to Section 8 of ICH E6 for a list of the minimum requirements.

**Document Tracking Log**

- Document Tracking Log
  - Is useful to ensure all controlled stationery is accounted for.

**Milestone Summary**

- Milestone Summary
  - Is useful at the front of each file and will ensure ALL of the team are aware what stage, amendment or version number the trial is working to.

**Study Specific Training Log**

- Study Specific Training Log
Is maintained at site and records all team members’ study specific training e.g., study set up meeting or consequent one-to-one training.

**Telephone Summary Template**

- Telephone Summary Template
  - It is a good idea to put telephone summary sheets by the phone, patient conversation/queries can be documented straight away.

**File Note Template**

- File Note Template
  - Can be used for any protocol deviations. Use to identify document location if not in Trial Master File or Case Report Form. This will ensure that everyone is clear at all times.

**Treatment Allocation Log**

- Treatment Allocation Log
  - Used by the Dr/Nurse to track and log how much IMP has been given, and when, to the subject at each visit. This log can be very useful if different members of staff are working on the same study. Pharmaceutical companies usually supply this log, but not always. It can be put at the front of the CRF for easy use.

**Appointment Checklist**

- Appointment Checklist
  - A simple, practical tool that enables any member of staff to prepare for the smooth running of the next planned visit. This form is very useful to plan and record the arrangement of all visit requirements, e.g., transport, ECG, staff time.
Study Supplies Issues Log

- Study Supplies Issues Log
  - Similar to the Treatment Allocation Log (above), but relating only to the SUPPLIES needed/used, eg needles, blood tubes, strips etc, so the supplies can be tracked from dispensing to having them when a subject returns for a visit.

Study Patient Visit Schedule

- Study Patient Visit Schedule
  - This log helps predict when each subject is due for their next visit to ensure they are not out of the visit schedule as per protocol (avoiding a serious breach!) It can be used as a tracker for active subjects, subjects in follow up or those who have withdrawn. Pharmaceutical companies usually supply this log, but not always. It can be put at the front of the CRF for easy use.
GCP: The Standards and Why We Have Them

Definitions

Good Clinical Practice (GCP)

- A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (As per Section 1.24 of ICH E6).

- Good clinical practice is a set of internationally recognised ethical and scientific quality requirements, which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible (As per Article 1.2 of 2001/20/EC).

Historical Foundation: Why Do We Need These GCP Standards?

The following reference list is by no means exhaustive. It is provided to help the reader understand some of the human atrocities and tragedies that led to the development of the bioethical guidelines and regulations we know nowadays as “Good Clinical Practice”.

GCP History: The Nazi ‘Medical’ Experiments

During the Second World War (1939 to 1945), the German Nazi’s performed many medical experiments on prisoners with a view to either ‘advancing science’ or aiding their soldiers in the battle.

Many of these experiments were terminal, none were in the best interests of those subjected to the experiments and none of the prisoners had a choice as to whether they would participate or not.

At the end of the Second World War some of the Nazi doctors who had performed human experiments were tried at a war crimes tribunal in Nuremburg. During the Nuremberg War Crime Trials, the ‘Nuremberg code’ was drafted as a set of standards for judging physicians...
and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype/foundation of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner (*The Belmont Report*).

- **Further Information can be found at:**
  - United States Holocaust Memorial Museum: [Nazi Medical Experiments](#)
  - CANDLES Holocaust Museum and Education Centre
  - [The Mengele Twins and Human Experimentation: A Personal Account](#)

- **Recommended Reading:**

**GCP History: The Tuskegee Syphilis Study**

In 1932 the US Government misled 623 African-Americans into participating into a study of untreated syphilis. The government induced these men to participate in a study in which the government represented that the participants were being treated for whatever their ailments were. They were never told what their ailment was. They never gave their consent to be involved in a study, nor did they realise they were part of a study until the story broke in July 1972. Treatment was knowingly withheld for 40 years (Fred D Gray – Attorney, 8th April 1997)*.

The public outcry from this study resulted in the drafting of the *Belmont Report* in 1979 on the ‘Ethical Principles and Guidelines for the Protection of Human Subjects of Research’ and in a [Presidential Apology in 1997](#).

- **Further information can be found at:**
  - [The Tuskegee Syphilis Study](#)
  - [U.S. Public Health Service Syphilis Study at Tuskegee](#)
  - [Tuskegee University - Research Ethics: The Tuskegee Syphilis Study](#)
  - [The Belmont Report](#)

• Recommended Reading:
  - Fred D Gray was the attorney for the men of the Tuskegee study

GCP History: Thalidomide

Thalidomide (alpha-phthalimido-glutarimide) was developed by the German firm Chemie Grunenthal as an anticonvulsant drug. Early trials showed it to be unsuitable for this purpose but indicated that it had sedative properties. Furthermore, it had one remarkable property: overdoses simply caused prolonged sleep, not death (Smithells & Newman, 1992).

In the mid-1950s there were no guidelines for the development, production and marketing of medicinal products, no uniform federal medicines act, and no licensing authority such as the present Federal Institute for Drugs and Medical Devices (BfArM), it was therefore possible to introduce thalidomide on the German market on 1st October 1957 without any governmental review of the documentation (The Thalidomide Tragedy – Grunenthal).

The drug was first marketed in Germany in 1957 under the name Contergan, and in the UK in April 1958 as Distaval. Later, compound preparations, which combined thalidomide with other drugs, were marketed for a wide variety of indications: Asmaval for asthma, Tensival for hypertension, Valgraine for migraine, and so forth. The promotion of these products laid great stress on the safety of thalidomide, based on the remarkable property described above (Smithells & Newman, 1992).

Between 1958 and 1961, the drug thalidomide was used by expectant mothers to control the symptoms of morning sickness. Tragically, this led to many babies being born with often severe physical disabilities (Commons Hansard: Statement - Thalidomide survivors – 14th January 2009).

The suffering experienced by people who took thalidomide during the period from 1957 to 1961 is incalculable. The reported number of those harmed varies, but more recent scientific studies indicate that 10,000 people worldwide were affected (The Thalidomide Tragedy – Grunenthal).

The first European Community Pharmaceutical Directive (65/65/EEC) was issued in 1965. Much of the impetus behind Directive 65/65/EEC stemmed from a determination to prevent a recurrence of the thalidomide disaster in the early 1960. This experience, which shook
NIHR CRN Good Clinical Practice Reference Resource

public health authorities and the general public, made it clear that to safeguard public health, no medicinal product must ever again be marketed without prior authorisation.


On the 14th January 2010 Health minister Mike O'Brien expressed the government's "sincere regret and deep sympathy" for victims of the drug thalidomide.

It comes four decades after expectant mothers suffering from morning sickness took the drug between 1958 and 1961. Thousands of their offspring suffered from physical disabilities as a result.

Of them, 466 members of the UK’s Thalidomide Trust remain. The government has announced a £20 million three-year pilot scheme, which will meet survivors' needs "in a more personalised way".

Mr O'Brien told MPs: "The government wishes to express its sincere regret and deep sympathy for the injury and suffering endured by all those affected when expectant mothers took the drug thalidomide between 1958 and 1961."

"We acknowledge both the physical hardship and the emotional difficulties that have faced both the children affected and their families as a result of this drug, and the challenges that many continue to endure, often on a daily basis."

The new funding for 'thalidomiders' will prioritise looking after their health needs for the long-term.

After the drug's negative side-effects were first realised the government launched a major review of the machinery for marketing, testing and regulating drugs, which resulted in the Medicines Act 1968.

(Source: Thalidomide UK Website)

• Further Information can be found at:
Current Situation: We Still Need These GCP Standards!

The following resources (articles, letters and reports) are provided as an illustration of what happens when the GCP standards aren’t applied and highlight, tragically in some cases, the fact that we still need these standards today.

Man Dies in Government Cancer Drug Trial (Oct 2007)

  - The mother of a 27-year-old man who died during a cancer drugs trial said she felt like he had been murdered.
  - Gary Foster, from Waltham Abbey, Essex, was given double the amount of chemotherapy he should have been prescribed for testicular cancer.
  - His mother Coleen Foster said he was due to get married this month and had everything to live for.
  - University College London Hospital blamed the death on a computer system error in the set-up of the trial.
The hospital said it had reviewed its drugs testing procedures and processes and had "made all appropriate changes to improve patient safety in response to this accident".

- Epping Forest News: WALTHAM ABBEY - Dashed hopes of drug trial death family (6 Jan 2011)
  - A CANCER patient who died during a drug trial hoped that the treatment would help him beat his disease, according to his family's solicitor.
  - Gary Foster, of Roundhills in Waltham Abbey, died at University College London Hospital (UCLH) in October 2007, after being given twice the correct dosage of chemotherapy drugs on several occasions.
  - Mr Foster, who was 27, entered the clinical trial in June that year, after being diagnosed with testicular cancer.
  - This week the family accepted around £300,000 in damages from the hospital's trust, which blamed the overdose on a computer error and said it had made changes to its procedures in the wake of Mr Foster's death.
  - Mark Bowman of Field Fisher Waterhouse, the family's solicitor, said: “We can confirm that a settlement has been reached in this case.
  - “This tragic case revealed a systematic failure in the setting up, running and monitoring of the TE23 trial at University College London Hospitals.
  - “Mr Foster enrolled on the trial in the hope that it would improve his chances of successfully recovering from testicular cancer.
  - “Unfortunately, due to the negligent treatment he received, one of the very drugs that was helping to cure his cancer caused irreparable damage to his lungs and ultimately resulted in his death.”

- Pharmatimes Report: Cancer trial death was a prescribing error, stresses MRC (22 Sept 2008)
  - The UK's Medical Research Council (MRC) has defended its role in a cancer trial sponsored by the Council in which a patient died last year after receiving an accidental overdose of the chemotherapy drug bleomycin.
  - In particular the MRC has stressed that the incident occurred as a result of an error in the computer prescribing system at University College London Hospital (UCLH), where Gary Foster was taking part in the trial. This error was a departure from the trial protocol (which is the sponsor’s responsibility) and
“does not call into question the safety of the treatment regimens” used, it said. Both the MRC and UCHL have since reviewed and amended their trial procedures.

- Read the full story at: [http://www.pharmatimes.com/Article/08-09-22/Cancer_trial_death_was_a_prescribing_error_stresses_MRC.aspx](http://www.pharmatimes.com/Article/08-09-22/Cancer_trial_death_was_a_prescribing_error_stresses_MRC.aspx)

- **Telegraph Report: Man Dies in Government Cancer Trial (21 Sept 2008)**
  - Gary Foster, 27, was repeatedly given twice the amount of chemotherapy drugs he should have been prescribed.
  - He was due to be married this month.
  - Reports have said his death was caused by an error in the setting up of the trial on the computer system at University College London Hospital (UCLH).
  - A second patient was affected by the same mistake, but survived.
  - When the MRC suspected patients had been given overdoses, instead of calling the hospital immediately it wrote a letter - which a nurse at UCLH failed to open until two days after Mr Foster had died.


**US Investigator’s Lack of Oversight has Tragic Results (2009)**

According to the warning letter sent to Dr Picus on 20 Sept 2010:

- **Study Oversight:**
  - You failed to personally conduct or supervise the clinical investigation
  - Your failure to adequately supervise led to significant problems with the conduct of the study

- **Protocol Compliance:**
  - You failed to ensure that the investigation was conducted according to the investigational plan, and you failed to protect the rights, safety, and welfare of the subjects under your care
  - The patient died
• **Informed Consent:**
  
  – You failed to obtain informed consent in accordance with the applicable provisions
  
  – You acknowledge that you failed to obtain written consent from the subject prior to conducting all screening procedures, but that you documented the subject’s verbal consent process in study records. The regulations require that informed consent be signed and dated by the subject or the subject’s legal representative prior to the subject’s involvement in the investigation. Failing to obtain adequate informed consent jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

• **Essential Documents (Drug Accountability):**
  
  – You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects

**Recent Examples of GCP Inspection Findings and GCP Misconduct**

• **MHRA (GCP) Website**
  
  o The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government body, which was set up in 2003 to bring together the functions of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA).
  
  o The MHRA is the UK Competent Authority responsible for the regulation of medicines (which includes the regulation of clinical trials) and medical devices and equipment used in healthcare and the investigation of harmful incidents. The MHRA now also looks after blood and blood products, working with UK blood services, healthcare providers, and other relevant organisations to improve blood quality and safety.

  • **Good Clinical Practice: Risk Based Inspections**

  • The GCP Risk Based Inspection Process commences for all organisations (sponsors, contract research organisations, hosting trial sites) that are engaged in clinical trial activities in
the UK, from **15 May 2009**. It uses a combination of information provided to the MHRA on the Compliance Report, internal information about previous inspection history, organisational changes and other compliance reports with the results of intelligence gathering to determine an organisation’s control of their risk.

- The resulting risk assessments will be categorised into high, medium and low risk and inspections prioritised for the companies with the highest risk category. For internal control purpose, a small proportion of organisations from the medium and low risk categories will be randomly selected for inspection. Inspections will be planned according to how much inspection resource is available in the upcoming year. The results of the compliance report being used to determine an approximate amount of inspection time required to perform the inspection.

- Completion of the Compliance Report by sponsors, contract research organisation (CRO) or hosting sites is not mandatory. However, these organisations should be aware that failure to submit a Completed Report will be assigned to a high risk category. Currently, Phase 1 units and individual investigators not acting as sponsors of clinical trials are not required to complete the compliance report.

- **The GCP Inspection Process**
- **MHRA GCP Inspection Findings Classification**
- **MHRA GCP Inspection Report Metrics**
  - **April 2007 to March 2008**
  - **Summary of MHRA GCP Inspection Findings 2006 - 2007**

- **US FDA** - [Inspections, Compliance, Enforcement, and Criminal Investigations: Warning Letters](#)
  - This website provides copies of warning letters sent by the FDA to individuals and organisations that have infringed food or drug Federal Regulations. These include GCP infringements and misconduct, such as:
- **Dr. Martin Zaiac (23 March 2011)**, who failed to:
  - Personally conduct or supervise the trial
  - Ensure the study was conducted according to the [protocol]
  - Maintain adequate and accurate case histories
  - Obtain informed consent in accordance with the relevant legislation
  - Ensure the REC was GCP compliant

- **Dr. Jeffrey Horowitz (23 March 2011)**, who failed to:
  - Retain records for the required period
  - Prepare and maintain adequate and accurate case histories
  - Ensure that the trial was conducted according to the [protocol]
  - Maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects
Global Clinical Trial Guidelines

There is a confusion of clinical research regulations and guidelines ‘out there’ that you, as a clinical researcher, need to be aware of, but also where applicable, to comply with. GCP training should aim to remove the ‘confusion’ element and show you how these regulations and guidelines fit together so that you will not only understand the letter of the law but also the spirit of the intentions of GCP, which is ultimately to prevent a reoccurrence of the atrocities performed during the Second World War, whether by the Nazi’s or by Japan’s infamous Unit 731. An overview of how these regulations and guidelines fit together in the UK can be found in the ‘CHCUK GCP Maps’.

Nuremberg Code (1947)

- Nuremberg Code (1947)
  - At the end of the Second World War some of the Nazi doctors who had performed human experiments were tried at a war crimes tribunal in Nuremburg. During the Nuremberg War Crime Trials, the ‘Nuremberg code’ was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype/foundation of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner (The Belmont Report).
  - The Nuremberg Code consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. The Nuremberg code includes such principles as informed consent and absence of coercion, properly formulated scientific experimentation, and the voluntary nature of the experiments.

UN Declarations of Human Rights

UN Declaration of Human Rights (1948)

- UN Universal Declaration of Human Rights (1948)
  - Have you ever wondered where the UK’s Human Rights Act came from and why? The United Nations “Universal Declaration of Human Rights” is the foundational
document that was created in response to the Nazi atrocities of the Second World War and eventually led to the Human Rights Act we have in the UK today.

- Refer also to the historical information on the Declaration of Human Rights contained in the UN Audiovisual Library of International Law.

**UN Declaration on Bioethics and Human Rights (2005)**

- [UN Declaration on Bioethics & Human Rights (2005)]

**UN Declarations on Human Genetic Data and Human Rights (1997 & 2003)**

- [UN Declaration on Human Genetic Data (2003)]
- [UN Declaration on the Human Genome and Human Rights (1997)]


- [Declaration of Helsinki (1996, 2000, 2008)]

  - The ethical principles set out in the Nuremberg Code have been further elaborated and clarified by the World Medical Association (WMA) through the document known as the 'Declaration of Helsinki', which has evolved since its inception in 1964 to its current form, which was published in 2008.

  - The Declaration of Helsinki is a very important document (in spite of recent controversies) because it provides the ethical foundation for ICH E6 (ICH GCP) (refer to Section 2.1 of ICH E6), the European Clinical Trial Directive (2001/20/EC) and GCP Directive (2005/28/EC) and national clinical research legislation (refer to Table 1). Everyone involved in clinical research should be encouraged to read this short document.

- **The reader may find the following resources helpful:**

Refer specifically to Chapter 6 (Research in developing countries: New ethics and new threats to human rights), which discusses the controversy over the recent Declaration of Helsinki standards.

Table 1 - Which Version of the Declaration of Helsinki Should I Use?

The following table provides an overview of the version of the Declaration of Helsinki currently referenced in the applicable clinical trial guidelines, Directives and laws.

<table>
<thead>
<tr>
<th>Region</th>
<th>Legislation</th>
<th>Relevant Section</th>
<th>DOH Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA/EU/Japan</td>
<td>ICH E6</td>
<td>Section 2.1</td>
<td>Not Specified</td>
</tr>
<tr>
<td>USA</td>
<td>21 CFR 312</td>
<td>Part 120</td>
<td>Reference to the 1969 version of the Declaration has been removed and replaced with a reference to “Good Clinical Practice”</td>
</tr>
<tr>
<td>EU</td>
<td>2001/20/EC</td>
<td>Recital 2</td>
<td>1996</td>
</tr>
<tr>
<td>EU</td>
<td>2005/26/EC</td>
<td>Article 3</td>
<td>1996</td>
</tr>
<tr>
<td>EU</td>
<td>2003/94/EC</td>
<td>Not Mentioned – Refers to 2001/20/EC</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>EU</td>
<td>2001/83/EC</td>
<td>Annex I, Recital 8 States “Clinical Trials must comply with the requirements of Directive 2001/20/EC”, which would infer the 1996 version of the DOH unless otherwise specified</td>
<td>Not Specified</td>
</tr>
<tr>
<td>UK</td>
<td>SI 2004/1031</td>
<td>Schedule 1, Part 1.2 Schedule 1, Part 2.6</td>
<td>1996</td>
</tr>
</tbody>
</table>

ICH Guidelines

What is the ICH?

The realisation that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. However in many cases the realisation was driven by tragedies, such as that with thalidomide in Europe in the 1960s (About the ICH).

For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. The industry, at the time, was becoming more international and seeking new global markets, however the divergence in technical requirements from country to country was such that
industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally (About the ICH).

The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of health care, escalation of the cost of R&D and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need (About the ICH).

Initiation of ICH

Harmonisation of regulatory requirements was pioneered by the European Community (EC), in the 1980s, as the EC (now the European Union) moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. At the same time there were bilateral discussions between Europe, Japan and the US on possibilities for harmonisation. It was, however, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialise. Soon afterwards, the authorities approached IFPMA to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived (About the ICH).

The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH (About the ICH).

At the first ICH Steering Committee (SC) meeting of ICH the Terms of Reference were agreed and it was decided that the Topics selected for harmonisation would be divided into Safety, Quality and Efficacy to reflect the three criteria, which are the basis for approving and authorising new medicinal products (About the ICH).

The Evolution of ICH

For two decades the ICH process has achieved much success. This success is attributed not only to a process of scientific consensus developed between industry and regulatory experts, but also to the commitment of the regulatory parties to implement the ICH Tripartite Harmonised Guidelines and recommendations (About the ICH).

Since ICH's inception in 1990, the ICH process has gradually evolved. ICH's first decade saw significant progress in the development of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics. Work was also undertaken on a number of important multidisciplinary topics, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document). As ICH started into a new millennium, the need to expand
communication and dissemination of information on ICH Guidelines with non-ICH regions became a key focus. Attention was also directed towards facilitating the implementation of ICH Guidelines in ICH’s own regions (About the ICH).

Throughout the second decade the development of ICH Guidelines continued, but with more attention given to the need to maintain already existing Guidelines as science and technology continued to evolve. The need to leverage with other organisations was also acknowledged, particularly for the development of electronic standards. The SC recognised the benefits afforded by collaboration with Standards Development Organisations, not only from the perspective of having a larger available pool of technical expertise, but also the opportunity to progress ICH standards as global standards (About the ICH).

Entering into its third decade of activity, ICH’s attention is directed towards extending the benefits of harmonisation beyond the ICH regions. Training, as well as active participation of non-ICH regions in guideline development, are seen as key in this effort (About the ICH).

ICH E6 (GCP) Guidelines

- **ICH E6**: Guideline for Good Clinical Practice
  
  - Also known as ‘ICH GCP’. This is very much the ‘Clinical Trial Bible’, the contents of which have been implemented into the European clinical trial quality standards through the Clinical Trials Directive ([2001/20/EC](http://example.com)) and the GCP Directive ([2005/28/EC](http://example.com)). The content of these Directives has in turn been transposed into national law by each of the Member States e.g., The Medicines for Human Use (Clinical Trials) Regulations of 2004 ([SI 2004/1031](http://example.com)) in the UK.
  
  - Particular attention is drawn to the following areas which are primarily and solely dealt with in ICH E6:
    
    - The Investigators Brochure (Section 7)
    - The Protocol (Section 6)
    - Monitoring (Section 5.18)
    - The Trial Master File (TMF) and Essential Documents (Section 8)

The ICH Efficacy (E) Series
The ICH "Efficacy" Topics, i.e., those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)

**Clinical Safety**

- **ICH E1**: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions
- **ICH E2A**: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- **ICH E2B**: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
  - ICH E2B – Questions and Answers
- **ICH E2C**: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
  - Addendum to E2C: Periodic Safety Update Reports for Marketed Drugs (in E2C(R1))
- **ICH E2D**: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
- **ICH E2E**: Pharmacovigilance Planning
- **ICH E2F**: Development Safety Update Report

**Clinical Study Reports**

- **ICH E3**: Structure and Content of Clinical Study Reports

**Dose-Response Studies**

- **ICH E4**: Dose-Response Information to Support Drug Registration

**Ethnic Factors**

- **ICH E5**: Ethnic Factors in the Acceptability of Foreign Clinical Data
  - ICH E5 – Questions and Answers
Good Clinical Practice

- **ICH E6**: Good Clinical Practice

Clinical Trials

- **ICH E7**: Studies in Support of Special Populations: Geriatrics
  - **ICH E7 – Questions and Answers**
- **ICH E8**: General Consideration of Clinical Trials
  - This is a very helpful document that describes the general principles of clinical trials from Phase 1 through to Phase 4, as well as, the considerations for individual clinical trials such as the design, conduct and reporting of clinical trials.
- **ICH E9**: Statistical Principles for Clinical Trials
- **ICH E10**: Choice of Control Group and Related Issues in Clinical Trials
- **ICH E11**: Clinical Investigation of Medicinal Products in the Paediatric Population

Guidelines for Clinical Evaluation by Therapeutic Category

- **ICH E12**: Principles for Clinical Evaluation of New Antihypertensive Drugs

Clinical Evaluation

- **ICH E14**: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
  - **ICH E14 – Questions and Answers (June 2008)**
  - **ICH E14(R1) – Questions and Answers (Concept Paper)**

Pharmacogenomics

- **ICH E15**: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
- **ICH E16**: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions
  - [Audio presentation on E16](#)

**OHRP International Compilation of Human Research Subjects Protections**

- **OHRP International Compilation of Human Research Subjects Protections**
  (Consolidated Summary of International Human Research Regulations)
  - This is a very useful document which has been developed by the Office for Human Research Protections (OHRP) in the USA which contains a summary of, and hyperlinks to, international regulations related to the various aspects of human research i.e., from clinical trials, genetic research, human tissue research etc. This report is updated annually.


  - This handbook is issued as an adjunct to WHO’s “Guidelines for good clinical practice (GCP) for trials on pharmaceutical products” (1995), and is intended to assist national regulatory authorities, sponsors, investigators and ethics committees in implementing GCP for industry sponsored, government-sponsored, institution-sponsored, or investigator-initiated clinical research.
Clinical Trials in Europe: Governance, Regulations and Guidelines

The European Union: Who are the Member States?

- EUROPA Website: Member States of the European Union

  - EUROPA is the portal site of the European Union (http://europa.eu). It provides up-to-date coverage of European Union affairs and essential information on European integration. Users can also consult all legislation currently in force or under discussion, access the websites of each of the EU institutions and find out about the policies administered by the European Union under the powers devolved to it by the Treaties.

European Commission Guidance: Pharmaceuticals in the European Union

- European Commission: Pharmaceuticals in the European Union

Key European Legislation Applicable to Clinical Research

Key European Directives Applicable to Clinical Research

The reader should note that European Directives must be transposed in the form of binding national legislation i.e., they aren’t a ‘stand alone’ legal document. Therefore, in essence a European Directive should be seen as a legal document, which ‘directs’ the member state to transpose (as a minimum) the contents of the Directive into national legislation, such as Statutory Instruments in the UK. Which is why the contents of the UK’s Medicine for Human Use (Clinical Trial) Regulations 2004 (SI 2004/1031) mirror those of the Clinical Trials Directive (2001/20/EC). However, the MHRA has not only taken the contents of the Clinical Trials Directive and drafted it in to a legally binding document (SI 2004/1031) but has also added to (and continues to add to) this minimum requirement to ensure that the clinical trial framework in the UK is robust.

Refer to the European Parliamentary Fact Sheet on the ‘Sources and Scope of European Union Law’ for further details on the European legal system.

- 2001/20/EC (Clinical Trials Directive)
Key European Regulations Applicable to Clinical Research

The reader should note that European Regulations apply directly in all the Member States without requiring a national act to transpose them. For example, the Paediatric Regulations (EC/1901/2006) are applicable to, and enforceable within, the UK without the need to transpose them into an Act or a Statutory Instrument. These are very much a ‘what you see is what you get’ form of legislation. There is no need for a corresponding UK Paediatric Regulation. This is one of the reasons why the European Regulations are very detailed documents in comparison to the Directives.

Refer to the European Parliamentary Fact Sheet on the ‘Sources and Scope of European Union Law’ for further details on the European legal system.

  - Amended by:
  - Refer also to:
    - **MCRN Guide to the EU Paediatric Regulation**
European Commission: Clinical Trial Resource (Eudralex Volume 10)

Links to some but not all of the information contained on this website has been included for example purposes below. Please refer to the source website (Eudralex Volume 10) for a full listing of current contents.

- Eudralex Volume 10
  - The European Commission’s rules governing medicinal products in the European Union are compiled into 10 separate ‘volumes’. Volume 10 contains guidance documents, which are applicable to clinical trials. This is a very important ‘one-stop-shop’ for all of the European regulations and guidelines applicable to clinical trials and includes:
    - Chapter I: Application and Application Form
      - Refer to link above for a full listing of contents
      - ENTR/CT1: Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (March 2010)
        - Annex 1: "Clinical trial application form" (March 2010)
        - Please note: Recent changes in the regulatory framework for pharmaceuticals and clinical trials in the EU (mainly consequences of the paediatrics legislation and the legislation on advanced therapies) have required changes to the clinical trials application form. This is the revised version of the clinical trials application form. It will become applicable in the course of the first half of 2010, and is published in advance to allow stakeholders time for preparation. A precise date for applicability is going to be published on this website
          - Annex 2: "Substantial Amendment Form" (June 2010)
          - Annex 3: "Declaration of the end of the trial" (June 2010)
• **ENTR/CT2**: Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (Feb 2006)

• **ENTR/CT5**: Detailed guidance on the European clinical trials database (EUDRACT Database) (April 2004)

### Chapter II: Monitoring and Pharmacovigilance

• Refer to link above for a full listing of contents

• **ENTR/CT3**: Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (April 2006)

• **ENTR/CT4**: Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance - Clinical Trial Module) (April 2004)

• **ENTR/F/2/SF/dn D(2009) 40108**: Questions & Answers Specific to Adverse Reaction Reporting in Clinical Trials. Version 1.0 (December 2009)

### Chapter III: Quality of the Investigational Medicinal Product

• Refer to link above for a full listing of contents

• **Annex 13**: Good Manufacturing Practices for Manufacture of Investigational Medicinal Products (Feb 2010)

• **CHMP/QWP/185401/2004**: Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials

• **Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (Mar 2011)**
  
  o This document intends to clarify and provide additional guidance on the definition of investigational medicinal products and to provide specific guidance about the use of non-investigational medicinal products (NIMPs), in accordance with the applicable EU legislation.

### Chapter IV: Inspections
• Refer to link above for a full listing of contents

  ▪ **Chapter V: Additional Information**

  • Refer to link above for a full listing of contents

  • **ICH E6**: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95

  • **ENTR/F/2/SF/dn D(2009) 35810**: Detailed Guidelines on Good Clinical Practice Specific to Advanced Therapy Medicinal Products (Dec 2009)

  • **Recommendation on the Content of the Trial Master File and Archiving (July 2006)**

  • "**Questions & Answers**" Document - Version 8 (March 2011)
    o The Annex to this document provides an algorithm to help determine whether your study is a clinical trial or a “Non-Interventional Clinical Trial”

  • **Guideline 2008/C168/02 on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products (July 2008)**

  • **ENTR/F/2/SF D (2009) 3687**: List of fields contained in the 'EudraCT' clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004 and its implementing guideline 2008/C168/02 (February 2009)

  • **Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA)**

  • **ENTR/F/2/SF/jr D (2009) 3698**: List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006 and its implementing guideline 2009/C28/01

  ▪ **Chapter VI: Legislation**

  • Refer to link above for a full listing of contents
Refer also to Eudralex Volume 1

- 2001/20/EC (Clinical Trials Directive)
- 2005/28/EC (GCP Directive)
- 2003/94/EC (GMP Directive)
Clinical Trials in the UK: Governance, Regulations and Guidelines

The UK Regulatory Authority (MHRA)

- The Medicines and Healthcare products Regulatory Agency (MHRA)
  - MHRA (GCP) Website

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  - The GCP Inspection Process
  - MHRA GCP Inspection Findings Classification
  - MHRA GCP Inspection Report Metrics
  - April 2007 to March 2008
     - Summary of MHRA GCP Inspection Findings 2006 - 2007

The UK Research Ethics Service (NRES)

- NRES Website (Home)
- NRES Website (Guidance Documents)
- NRES SOP (May 2010) - Standard Operating Procedures for Research Ethics Committees

The UK’s Research Governance Framework

ALL research involving NHS patients, staff or resources must be assessed by a research ethics committee. Furthermore, to comply with the Department of Health’s Research Governance Framework all such research activities must be formally approved by NHS R&D Trust management.
  
  o The Research Governance Framework for Health and Social Care (RGFHSC) sets out the broad principle of good research governance.

• **Research Governance Framework (Second Edition) Annex**
  
  o The annex lists detailed principles and requirements for different aspects of research governance. It includes legislative requirements, Department of Health requirements, and statements of recognised good practice from a variety of established sources.

  o Health and social care research is not the province of a single discipline, profession or organisation and no single document adequately captures the full range of legislation, standards and good practice guidelines that apply to this wide-ranging body of work.

  o They are presented here in five domains. Where available, the annex includes website addresses for the current standards, legislation and guidance listed in the domains. Where these relate to more than one domain they have been cross-referenced.

    ▪ **A: Ethics and patient information**
    
    ▪ **B: Science**
    
    ▪ **C: Information**
    
    ▪ **D: Health, safety and employment**
    
    ▪ **E: Finance and intellectual property rights**

**Governance, Advice and Ethics Systems**

The [NIHR](https://www.nihr.ac.uk) is working to simplify and streamline administrative and regulatory procedures governing research trials and studies.

The key initiatives are:

• **Ensuring good governance through networks**
  
  o A national unit in the [NIHR Clinical Research Network Coordinating Centre](https://www.nihr.ac.uk/crns) (NIHR CRN CC) coordinates R&D management. A key function of the [NIHR Comprehensive Research Network](https://www.nihr.ac.uk/crns) (CRN) is excellent R&D management to
deliver proper governance. It helps researchers deal with regulatory,
governance and ethics procedures to consistently high standards,
safeguarding the rights, safety, dignity and well-being of people who take
part. The research-active NHS organisations in the CRN work together as a
national research management and governance service, sharing common
procedures and integrated R&D information systems.

The national coordinating unit for research management and network became operational
in April 2007. The NIHR CRN implemented the Comprehensive Local Research
Networks (CLRNs) from 2007. To improve the quality, speed and efficiency
of research and research processes in the NHS, the NIHR is also facilitating
the reconfiguration of NHS R&D offices within a national framework for
research support services. This will harmonise and streamline the local
processes for funded health research in the NHS and build consensus on a
proportionate risk-based interpretation of policies and rules by NHS R&D
offices.

- Integrated Research Application System (IRAS)
  - IRAS is a single, integrated on-line application system. Launched in January
    2008, it streamlines the process for permissions and approvals to conduct
    health and social care research. Using IRAS, researchers can enter
    information about their study in one place. It is designed to save time and
    effort. Applicants no longer duplicate information in separate application
    forms for each type of approval. The system has prompts and an e-learning
    module to help them get it right.
  - The National Research Ethics Service developed IRAS with support from its
    partners including the NIHR. The Department of Health funds it. The IRAS
    team is preparing for an evaluation to inform future development.
  - Further information is available on my research project website.

- The NIHR Coordinated System for gaining NHS Permission (NIHR CSP)
  - In 2008, the NIHR launched a procedure to streamline local NHS permission
    so that clinical research studies can be approved much more quickly. This
    includes a 'one stop shop' and shared information systems, reducing
    bureaucracy for studies intended for the NIHR Portfolio. The NIHR CSP is
    now the standard method of providing and checking information on studies
    for adoption for the NIHR Portfolio. Investigators apply through the
    Integrated Research Application System. IRAS now provides a single point of
application for research regulation, approvals and local permission to start a study. From April 2009, NHS organisations have to use the NIHR CSP for NIHR portfolio studies if they are to qualify for NIHR clinical research network funding.

- Further information can be found on NIHR Clinical Research Network website.

**Research Passport**

- The research passport unifies and simplifies administrative procedures to make it easier and faster to begin agreed research studies. It is a streamlined approach to issuing honorary research contracts for researchers who have no contractual arrangements with the NHS but who carry out research in the NHS that can affect patient care.

- The NIHR developed the **Research in the NHS - Human Resource (HR) Good Practice Resource Pack**, with extensive support from the NHS R&D Forum working with partners in the UK Clinical Research Collaboration (UKCRC). After piloting in September 2006, the Pack was made generally available in 2007. The pack will be revised from time to time.

- The Department of Health recommends the Research Passport to the NHS, Higher Education Institutions (HEIs) and other research employers working in partnership with the NIHR. The **UKCRC Partners** endorse the routine use of the Research Passport system.

- The resource pack provides guidance and good practice standards for the NHS and Higher Education, to achieve consistency in issuing and recognising NHS honorary research contracts. The Comprehensive Local Research Networks have adopted the Research Passport as standard practice.

- **Research Passport: Research in NHS - HR Good Practice Resource Pack**

**Regulatory and governance advice service**

- The Regulatory and Governance Advice Service is a national advice service of front-line advisers in the CLRNs, linked to national experts on regulatory processes, approvals and permissions. The NIHR and our partners developed and piloted an Advice Service for regulatory and governance issues under the auspices of the UK Clinical Research Collaboration (UKCRC). The Advice Service was expanded in 2007 to cover the whole of the UK. In England, it works locally through the Comprehensive Local Research...
Networks. The Regulatory and Governance Advice Service handles complex queries and those involving more than one regulatory issue. It is developing authoritative, web-based resources, such as tool kits and a new online Q&A, to share good practice, promote consistency and provide support to local R&D.

- Further information is available through the UKCRC.

- Research ethics
  - The National Research Ethics Service (NRES) was launched in April 2007. The HQ of the NRES at the National Patient Safety Agency is implementing measures that will give ethics committees expert support, and help simplify the review of low-risk studies and surveys. The implementation plan Building on improvement: Implementing the recommendations of the Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees was published in 2006.

- Promoting good research practice
  - The UK Research Integrity Office (UKRIO) pursues a programme of work to:
    - Promote the good governance, management and conduct of research;
    - Share good practice on how to address misconduct in research and;
    - Give advice and guidance on specific cases.
  - This has produced a Code of Practice (PDF), a procedure for investigating research misconduct (PDF) and a Research Integrity Helpline.
  - Further information about the ongoing programme of work is available from the UK Research Integrity Office.

Further Information and Resources


- Department of Health Website: Research Governance
  - Department of Health Website: Health-related Act and Bills
o Provides summaries of, and links to relevant healthcare-related Acts and Bills

- **NIHR Regulatory and Governance Advice**


  o Applicable to research conducted in Scotland

**The UK Integrated Research Application System (IRAS)**

*IRAS* is a single, integrated on-line application system. Launched in January 2008, it streamlines the process for permissions and approvals to conduct health and social care research. Using IRAS, researchers can enter information about their study in one place. It is designed to save time and effort. Applicants no longer duplicate information in separate application forms for each type of approval. The system has prompts and an e-learning module to help them get it right.

- **The Integrated Research Application System (IRAS):**

  o Is a single system for applying for the permissions and approvals for health and social care / community care research in the UK

  o Enables you to enter the information about your project once instead of duplicating information in separate application forms

  o Uses filters to ensure that the data collected and collated is appropriate to the type of study, and consequently the permissions and approvals required

  o Helps you to meet regulatory and governance requirements

  o Retains familiar aspects of the NRES form system

- **IRAS** captures the information needed for the relevant approvals from the following review bodies:

  o Administration of Radioactive Substances Advisory Committee (ARSAC)

  o Gene Therapy Advisory Committee (GTAC)
There is sometimes confusion regarding which regulations and guidelines we should follow when conducting clinical trials. In the UK, the answer is reasonably simple. When conducting clinical trials, we conduct them in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which implement the Clinical Trials Directive (2001/20/EC) into UK law and which has been amended over the years to implement the GCP Directive (2005/28/EC) and capture elements of ICH E6 that weren’t included in these Directives, such as non-compliance with the protocol.

The legal basis for the conduct of clinical trials in the UK is always the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). However, it should be noted that Part 2.8 of Schedule 1 of Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) requires that:

“The Investigator and Sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial”

Such ‘relevant guidance’ includes (but is not limited to) those published by the European Commission’s Rules Governing Medicinal Products in the European Union (Eudralex), which in turn are based on ICH E6 and ultimately the Declaration of Helsinki.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) do not contain all of the information necessary for running a clinical trial as this would make them unmanageable.

Examples of omissions include, but are not limited to:

- The role and responsibilities of a monitor;
- The format of the clinical study report, protocol and Investigators brochure; and
The contents of the Trial Master File.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) do provide the legal framework for the conduct of clinical trials in the UK and direct the trial Sponsors and Investigators to “consider all relevant guidance with respect to commencing and conducting a clinical trial”, which is why we regularly refer to ICH E6 (which is one source of the ‘relevant guidance’ referred to) when managing and conducting clinical trials.

Core Legislation Governing Clinical Trials in the UK

The following list captures the core legislation, which govern clinical trials in the UK.

- **The Medicines Act 1968**
  - As amended by the [Medicines Act 1971](#)
  - This reference has been included for the sake of completeness but with the implementation (and subsequent amendment of) [SI 2004/1031](#), this Act is no longer of direct relevance to the general conduct of clinical trials in the UK.

- **SI 2004/1031**: The Medicines for Human Use (Clinical Trials) Regulations 2004
  - This statutory instrument or ‘SI’ is often referred to as the ‘Principal Regulations’ and implements the Clinical Trials Directive ([2001/20/EC](#)) into UK law. All of the subsequent clinical trial statutory instruments have been amendments to this regulation.

- **SI 2006/1928**: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
  - This statutory instrument implemented the GCP Directive ([2005/28/EC](#)) into UK law. It also implemented the principle of ‘Serious Breach of GCP or the Protocol’ into UK law, which isn’t captured in letter of the Clinical Trials or GCP Directives but has always been part of ICH E6 (Refer to Section 5.20).

- **SI 2006/2984**: The Medicines for Human Use (Clinical Trials) Amendments (No.2) Regulations 2006

- **SI 2008/941**: The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008

- **SI 2009/1164**: The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009
• **SI 2010/1882**: The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010

• **CHCUK Summary and Overview of the Amendments to the UK Clinical Trial Regulations**
  
  o This short document provides the user with a pictorial overview of how the various UK clinical trial regulations and guidelines fit together and also provides a summary of the relevance of each of these statutory instruments to conducting clinical trials in the UK. Each map provides hyperlinks to all of the listed regulations and guidelines.

• **The UK Clinical Research Regulations: Consolidated and Indexed - Canary Ltd**
  
  o The UK clinical trial regulations can be quite confusing to understand as each new regulation which has been implemented since 2004 is an amendment to the original or ‘Principal’ 2004 regulations and therefore has to be read in conjunction with the Principal regulations and all of the subsequent amendments. This handy publication consolidates all of the regulations into one easy to read document.

• Refer to [Parliamentary Factsheet number L7 (Statutory Instruments)](http://www.parliament.uk) for an easy to understand guide on what a “Statutory Instrument” actually is.

### Public and Patient Involvement

• NIHR Website: [Patient and Public Involvement](http://www.nihr.ac.uk)
  
  o NIHR CRN CC aims to improve patient care and allow people across the country access to the best treatment. A common theme that runs throughout its work is Patient and Public Involvement (PPI) because NIHR CRN CC believes that active PPI is needed if it is to achieve a programme of research, which directly reflects the needs, and views of patients and the public.

• [INVOLVE Website](http://www.involve.org.uk)
  
  o INVOLVE is a national advisory group, funded by the National Institute for Health Research (NIHR). Its role is to support and promote active public involvement in NHS, public health and social care research.
Healthtalkonline Website

- Healthtalkonline is the award-winning website of the DIPEX charity and replaces the website formerly at dipex.org. Healthtalkonline lets you share in other people's experiences of health and illness. You can watch or listen to videos of the interviews, read about people's experiences and find reliable information about conditions, treatment choices and support.

- The information on Healthtalkonline is based on qualitative research into patient experiences, led by experts at the University of Oxford. These personal stories of health and illness will enable patients, families and healthcare professionals to benefit from the experiences of others.

Clinical Trials Involving Children

- The UK’s Medicines for Children Research Network (MCRN)
- MHRA Website: Medicines for Children
- European Commission Website: Medicines for Children
- European Commission Guidance Documents: Scientific Guidelines for Human Medicinal Products - Paediatrics

  - Refer specifically to:
    - Chapter 6: Clinical Trials in Children (By Vincent Yeung)
      - Link to Sample Text

Research Involving Mentally Incapacitated Subjects

Legislation: England
• **Mental Health Act 2007**
  - The Mental Health Act received Royal Assent on 19 July 2007. It amends the Mental Health Act 1983, and introduces "Bournewood" safeguards through amending the Mental Capacity Act 2005.

• **The Mental Capacity Act 2005**
  - Applicable to trial subjects in England & Wales
  - [Explanatory Notes: Mental Capacity Act (2005)]
  - [Code of Practice: Mental Capacity Act 2005]
  - The reader is urged to consider not only the Act (Primary Legislation) but also the relevant Statutory Instruments (Secondary Legislation), whether they be Rules, Regulations or Orders, which may contain relevant information not detailed in the Act itself (see below):

**Legislation: Scotland**

• **The Adults with Incapacity (Scotland) Act 2000**
  - Applicable to trial subjects in Scotland
  - [Adults with Incapacity (Scotland) Act 2000: General Information]
  - The reader is urged to consider not only the Act (Primary Legislation) but also the relevant Statutory Instruments (Secondary Legislation), whether they be Rules, Regulations or Orders, which may contain relevant information not detailed in the Act itself (see below):
    - [SSI 2002/190 (Scotland): Adults with Incapacity (Ethics Committee) (Scotland) Regulations 2002]
NRES Guidance: Adults Unable to Consent for Themselves

- National Research Ethics Service (NRES) Guidance:
  - Adults lacking capacity – on-line toolkit
    - An on-line toolkit on research involving adults lacking capacity to consent for themselves. The toolkit covers the provisions of the Mental Capacity Act 2005 and the separate provisions for medicinal trials under the Medicines for Human Use (Clinical Trials) Regulations 2004. It includes a specific module on research in emergency medicine.

- DH Mental Capacity Act 2005 guidance page (External link) Department of Health Mental Capacity Act 2005 guidance page

- Guidance on nominating a consultee for research Guidance on nominating a consultee for research involving adults who lack capacity to consent. (External link to DH)

- Informed consent in CTIMPs NRES information paper on informed consent in clinical trials of investigational medicinal products

- MCA1 - Supplementary Information Form MCA1 - Supplementary Information Form for approval under Section 30 of the Mental Capacity Act

- MCA2 - Supplementary Information Form for approval MCA2 - Supplementary Information Form for approval under Section 34 of the Mental Capacity Act

- Mental Capacity Act 2005 Mental Capacity Act (MCA) 2005

- Mental Capacity Act 2005 Questions and Answers Questions and answers on the Mental Capacity Act 2005, including principles, scope of the research provisions, applying for approval under the Act, approval criteria, consultees, loss of / regaining capacity during research.

- Mental Capacity Act Code of Practice (External link) Mental Capacity Act Code of Practice

- Mental Capacity Act Factsheet for Social Scientists Mental Capacity Act Factsheet for Social Scientists
• **Section 30 approval criteria** Criteria for approving research under sections 30-33 of the Mental Capacity Act 2005

• **Section 34 approval criteria** Criteria for approving research under section 34 of the Mental Capacity Act 2005

• **NRES Standard Operating Procedures for Research Ethics Committees (Version 4.1, May 2010)**
  
  o Refer specifically to:
  
  ▪ **Section 12**: Research Involving Adults Unable to Consent for Themselves

  • **Section 12.11 to 12.65**: Research Other than CTIMPs
    
    o Sections 30-34 of the Mental Capacity Act make detailed provision relating to research involving adults aged 16 or over who are unable to consent for themselves. The Act applies in England and Wales only. It has no application to CTIMPs.

    o The application of these provisions is not limited to medical and biomedical research, health-related research or research taking place within the NHS. It applies potentially to research in the context of social care and in any other context where participants could lack capacity to give informed consent.

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**Research Using Human Tissue**

**Legislation**

• **Human Tissue Act (2004)**
  
  o Applicable only to England, Wales and Northern Ireland

  o Refer also to the website of the Human Tissue Authority for further guidance

  o Refer to the ‘CHCUK Human Tissue Map’ for an overview of the regulatory framework in the whole of the UK, including hyperlinks to all of the relevant Acts and Statutory instruments.
The reader is urged to consider not only the Acts (Primary Legislation) listed below but also the relevant Statutory Instruments (Secondary Legislation), whether they be Rules, Regulations or Orders, which may contain relevant information not detailed in the Act itself, as is the case with the Human Tissue Act 2004. Refer to the ‘CHCUK Human Tissue Map’ for further details.

- **HTA Code of Practice 9 (Research)** – Human Tissue Authority’s (HTA) Code of Practice on Research using Human Tissue

- **Human Tissue (Scotland) Act 2006**
  - Applicable only to Scotland
  - **Note:** The sections of the Human Tissue Act 2004 which deal with ‘non-consensual analysis of DNA’ (Section 45 and Schedule 4) span all UK borders and also include Scotland
  - Refer to the ‘CHCUK Human Tissue Map’ for an overview of the regulatory framework in the whole of the UK, including hyperlinks to all of the relevant Acts and Statutory instruments.

  - The reader is urged to consider not only the Acts (Primary Legislation) listed below but also the relevant Statutory Instruments (Secondary Legislation), which may contain relevant information not detailed in the Act itself, as is the case with the Human Tissue Act 2004. Refer to the ‘CHCUK Human Tissue Map’ for further details.

**Regulatory Authority:** The Human Tissue Authority

- **The Human Tissue Authority (HTA)**
  - **HTA Codes of Practice**
    - The HTA’s revised codes of practice came into force on 15 September 2009.
    - The codes of practice provide guidance and lay down expected standards for each of the sectors we regulate. The revised codes are designed to support professionals by giving advice and guidance based on real-life experience. The codes were approved by Parliament
in July 2009 and have been brought into force via Directions 002/2009.

- **Code of practice 1 - Consent**
- **Code of practice 2 - Donation of solid organs for transplantation**
- **Code of practice 3 - Post-mortem examination**
- **Code of practice 4 - Anatomical examination**
- **Code of practice 5 - Disposal of human tissue**
  - PLEASE NOTE: the HTA has provided further clarification on the disposal of identifiable material and paragraph 73 in this code has been amended. This code does not require Parliamentary approval to have effect, so can be amended by the HTA as it feels appropriate.
- **Code of practice 6 - Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation**
- **Code of practice 7 - Public display**
- **Code of practice 8 - Import and export of human bodies, body parts and tissue**
- **Code of practice 9 - Research**

**MRC & Department of Health Resources**

- Medical Research Council and Department of Health: [Data and Tissues Tool Kit](#)
  - Provides practical guidance on using personal information and human tissue samples in research.

**Data Protection**
Legislation

- Data Protection Act (1998)

Regulatory Authority: ICO

- The Information Commissioner's Office (The UK’s Data Protection Agency)
  - ICO Notification handbook: A Complete Guide to Notification
  - ICO Guidance on the Data Protection Act

Department of Health Guidance

- Department of Health: Guidance to the NHS on the Data Protection Act 1998
- Department of Health Guidance: Research involving the NHS - Retention of Records (2007)
- Department of Health Guidance: Patient confidentiality and Access to Health Records

Information Governance: Caldicott Guardians

- Information Governance: Caldicott Guardians
  - Information Governance Training Tool
  - Caldicott Guardian Manual 2010
  - Caldicott – Principles into Practice (Welsh Version) 2008: A foundation manual and linked website providing Caldicott Guardians with knowledge
about the legal background to their role and its relationship with Information Governance.


### Fraud & Misconduct in Clinical Research

- **UKRIO Procedure for Investigating Research Misconduct**: The UK Research Integrity Office (UKRIO) - Procedure for the Investigation of Misconduct in Research
- **MHRA Website**: How to Report Breaches of the Trial or Protocol
- **Fraud Act 2006**
  - Explanatory Notes: Fraud Act 2006
    - The Act repeals all the deception offences in the Theft Acts of 1968 and 1978 and replaces them with a single offence of fraud (Section 1) which can be committed in three different ways by:
      - false representation (Section 2);
      - failure to disclose information when there is a legal duty to do so (Section 3);
      - abuse of position (Section 4).
    - The Act also creates new offences of possession (Section 6) and making or supplying articles for use in frauds (Section 7).
    - The offence of fraudulent trading (Section 458 of the Companies Act 1985) will apply to sole traders (Section 9).
    - Obtaining services by deception is replaced by a new offence of obtaining services dishonestly (Section 11).
- **MedicoLegal Investigations (MLI) Ltd**
The only UK company specialising in research fraud/misconduct investigations now supported by the Association of the British Pharmaceutical Industry.

Research fraud and misconduct can seriously affect the outcome of your clinical development programme. Identifying possible research fraud and then knowing how to investigate it are challenges for all pharmaceutical physicians and their colleagues who are involved in clinical research.

MLI provides training to the pharmaceutical industry and the NHS in the identification and investigation of research fraud and misconduct.

Take Heed of the Lessons Learned!

- Almost all the vital and conclusive evidence has been unearthed once the wall of confidentiality is penetrated. It is generally known that the MLI process is simply to ask health authorities to pass on letters to patients whose initials and dates of birth are known. We neither seek, nor are given, any information regarding the identity of patients. It is left to patients, once they have read a carefully worded letter, to respond or remain anonymous. Seventy percent respond. In paediatric cases we normally receive a one hundred percent response rate. The revelations in patient interviews are often astounding. It seems nothing is beyond possibility for a dishonest investigator - one has offered a patient £2000 not to respond to MLI, one had a married couple in the same depression study even though only the wife was diagnosed depressed; her husband was asked to participate to support his wife. Blinding envelopes have been found to be vulnerable - information within can easily be obtained without damaging seals. Nurses have been coerced into taking up to three ECG's at the same time from the same patient. Other wrongdoings involve falsifying medical records, inventing patients, splitting blood samples and so on (MedicoLegal Investigations Ltd).

UK Clinical Trial Resources

- Medical Research Council (MRC) Regulatory Support Centre: The MRC The Regulatory Support Centre (RSC) provides support and guidance for those conducting research with human participants, their tissues or data.

  Clinical Trial Toolkit
Guides you through the requirements when testing the safety or efficacy of a medicinal product. This site is currently under review by NIHR Clinical Research Network Coordinating Centre (NIHR CRN CC).

- **Data and Tissues Tool Kit**
  - Provides practical guidance on using personal information and human tissue samples in research.

- **Experimental Medicine Toolkit**
  - Covers a diversity of interventional studies, identifying appropriate regulatory frameworks & supporting a risk-based approach to study management.

**Interventional Clinical Trial (CTIMP) or Non-Interventional Trial (Non-CTIMP)?**

From the outset, it is important to determine whether the study that you plan to conduct is a non-interventional study or a clinical trial. Non-interventional studies (NIS) and clinical trials fall under distinctly different sets of regulations and guidelines within Europe. The Medicines and Healthcare products Regulatory Agency (MHRA) has devised a **useful algorithm to help differentiate between the two types of study**.

**ALL** research involving NHS patients, staff or resources must be assessed by a research ethics committee. Furthermore, to comply with the **Department of Health’s Research Governance Framework** all such research activities must be formally approved by Trust management.

  - This guidance has been collated by the NHS Research and Development Forum as an aid to researchers and NHS R&D staff in determining what projects should be managed in accordance with the Research Governance Framework in NHS organisations. The guidance has been developed following consultation with researchers, R&D managers, Clinical Effectiveness and Audit staff, and R&D Support Unit staff.
  - This document looks specifically at:
    - Research
    - Clinical Audit
- Student Research
- Clinical Investigation
- Case Studies/ Case Reports
- Data Management and Analysis
- Consensus Methods
- Service Evaluation
- Ethical Review of Research

**Definition: CTIMP and Non-CTIMP**

- **CTIMP**: Clinical trial of an investigational medicinal product (Any other type of research is known as a non-CTIMP).
- **Non-CTIMP**: Any research study that is not a CTIMP

(Source: NRES SOPS, Version 4.1, May 2010)

**Definition: Non-Interventional Study or Non-Interventional Trial**

- A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data (as per Article 2(c) of 2001/20/EC).

**Decision Algorithms: Clinical Trial? Non-Interventional Study? Research? Audit?**

- **MHRA Guidance: Is your Research Study a Clinical Trial or a Non-Interventional Clinical Trial?**
  
  o This is an important determination as the regulations which govern each of these types of study differ.
For further guidance refer to the ‘CHCUK NIS Regulatory Map’

- **NRES Guidance: Differentiating Audit, Service Evaluation and Research (April 2007)**
- **NRES Leaflet: Defining Research**

### Non-CTIMP and NIS Resources

  
  Refer specifically to:

  - **Section 1.14 & 1.15**: Non-Interventional Trials
  - **Section 1.18 & 1.19**: Allocation of Non-CTIMPs
  - **Sections 5.32 to 5.37**: Deciding Whether an Amendment is Substantial
  - **Section 12**: Research Involving Adults Unable to Consent for Themselves
    
    - **Section 12.11 to 12.65**: Research Other than CTIMPs
      
      - Sections 30-34 of the [Mental Capacity Act](#) make detailed provision relating to research involving adults aged 16 or over who are unable to consent for themselves. [The Act](#) applies in England and Wales only. It has no application to CTIMPs.
      
      - The application of these provisions is not limited to medical and biomedical research, health-related research or research taking place within the NHS. It applies potentially to research in the context of social care and in any other context where participants could lack capacity to give informed consent.

  - **Annex C**: Research in Human Subjects Other than Clinical Trials of Investigational Medicinal Products
    
    - This document sets out important guidance for sponsors and investigators on the conduct and management of research in human subjects (other than CTIMPs) with a favourable opinion from a NHS Research Ethics Committee. Please read the
guidance carefully. A failure to follow the guidance could lead to the Committee reviewing its opinion on the research.

- Department of Health Website: Research Governance

**CHCUK Resources: Non-Interventional Studies**

- CHCUK Website: Non-Interventional Studies
- CHCUK provide a range of tools and services which aim to help you understand the regulatory framework(s) within which NIS currently sit e.g., regulatory maps capturing the regulations and guidelines applicable to specific regions.
  - NIS Regulatory Maps
    - CHCUK 'Regulatory Maps' aim to provide the user with a pictorial overview of how the various regulations and guidelines fit together. Each map provides hyperlinks to all of the listed regulations and guidelines.
  - NIS Resources
    - NIS REPORT PART 1 - Considerations when Managing and Conducting NIS in Europe (Part 1)
      - Part 1 covers the NIS regulations and guidelines applicable to the following countries: Belgium, France, Germany, Greece, Poland, Portugal, Spain, Sweden, Switzerland, The Czech Republic, The Netherlands
    - NIS REPORT PART 2 - Considerations when Managing and Conducting NIS in Europe (Part 2)
      - Part 2 covers the NIS regulations and guidelines applicable to the following countries: Austria, Bulgaria, Cyprus, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Norway, Romania, Slovakia, Slovenia, and the UK
Study Set Up: Responsibilities, Approvals and Essential Documents

Definitions

Definition: Chief Investigator

- “chief investigator” means—
  
  - (a) in relation to a clinical trial conducted at a single trial site, the investigator for that site, or
  
  - (b) in relation to a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial (As per Regulation 2.1 of SI 2004/1031).

Definition: Good Manufacturing Practice (GMP)

- Good manufacturing practice means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use (As per Article 2.6 of 2003/94/EC).

Definition: Investigator

- A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (As per Section 1.34 of ICH E6).

- ‘investigator’: a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator (As per Article 2(f) of 2001/20/EC)
“investigator” means, in relation to a clinical trial, the authorised health professional responsible for the conduct of that trial at a trial site, and if the trial is conducted by a team of authorised health professionals at a trial site, the investigator is the leader responsible for that team (As per Regulation 2.1 of SI 2004/1031).

Definition: Investigator’s Brochure

- A Compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (As per Section 1.36 of ICH E6).
- ‘investigator’s brochure’: a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects (As per Article 2(g) of 2001/20/EC).
- “investigator’s brochure” means a document containing a summary of the clinical and nonclinical data relating to an investigational medicinal product which are relevant to the study of the product in human subjects (As per Regulation 2.1 of SI 2004/1031).

Definition: Investigational Medicinal Product (IMP)

- A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (As per Section 1.33 of ICH E6).
- ‘investigational medicinal product’: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (as per Article 2(d) of 2001/20/EC).
- “investigational medicinal product” means a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a
reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial—

- used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization,
- used for an indication not included in the summary of product characteristics under the authorization for that product, or
- used to gain further information about the form of that product as authorised under the authorization (As per Regulation 2(1) of SI 2004/1031).

Definition: Protocol

- A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol reference documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments (As per Section 1.44 of ICH E6).

- ‘protocol’: a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments (As per Article 2(h) of 2001/20/EC).

- “protocol” means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial (As per Regulation 2.1 of SI 2004/1031).

Definition: The Regulatory Green Light (RGL)

- Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step release procedure: certification by the Qualified Person; and release following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. The sponsor should ensure that these are consistent with the details actually considered by the Qualified Person. Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor (As per Paragraph 44 of Annex 13).
The Regulatory Green Light (RGL) Process is a 2-step release process, as described in Paragraph 44 of Annex 13.

Definition: Sponsor

- Any individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial (As per Section 1.53 of ICH E6).
- ‘sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial (As per Article 2(e) of 2001/20/EC).
- “sponsor” means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial (As per Regulation 3.1 of SI 2004/1031).

- Note – The definition of the “Sponsor of a Clinical Trial” is more detailed than provided for here. The reader is therefore strongly encouraged to read all of Regulation 3 of SI 2004/1031 as amended.

What Do I Need to Do to Start a Clinical Trial Within the UK?

The requirements of the Clinical Trial Regulations (SI 2004/1031 as amended) must be fulfilled; in general this means that a Clinical Trial Sponsor must be identified (Regulation 3) and authorisation sought from the Licensing Authority (the MHRA) and a favourable ethical opinion should be granted by a Recognised Ethical Committee (Regulation 12) (MHRA Website: GCP FAQs).

More information on the details required to complete a Licensing Authority approval application (Clinical Trial Application for Authorisation) and procedures for submitting an application to an Ethics Committee can be found at the NRES Website and through the links and information provided below.

The Clinical Trial Toolkit: Maps out the Application Process

- The Department of Health & Medical Research Council Clinical Trials Toolkit
  - Medical Research Council (MRC) and the Department of Health (DH) have developed this site to help you understand the clinical trial Regulations.
Applying for Authorisation to Conduct a Clinical Trial

- MHRA Website: Clinical Trials for Medicines – Applying to Conduct a Clinical Trial
  - MHRA Website: Clinical Trial Authorisations - Is a Clinical Trial Authorisation Required?

The UK Integrated Research Application System (IRAS)

The Integrated Research Application System (IRAS) now includes full functionality for studies involving investigational medicinal products (IMPs).

From 9th March 2009 all the data that are required to make an application to the Medicines and Healthcare products Regulatory Agency (MHRA) for authorisation of a clinical trial of an Investigational Medicinal Product (IMP) can now be completed within the Integrated Research Application System (IRAS). Previously IRAS only collected information about the IMP that was also required by other review bodies. That meant that although information could be imported and exported between IRAS and EudraCT, further information also needed to be completed in EudraCT before an application to the MHRA could be made. Now through IRAS all the information about a study can be entered in one place and researchers need only to go to EudraCT to obtain their EudraCT number. IRAS contains extensive guidance to support researchers in completing their application form. Additionally, it is now possible to generate the application form to the MHRA in the appropriate formats directly from IRAS.

- The Integrated Research Application System (IRAS):
  - Is a single system for applying for the permissions and approvals for health and social care / community care research in the UK
  - Enables you to enter the information about your project once instead of duplicating information in separate application forms
  - Uses filters to ensure that the data collected and collated is appropriate to the type of study, and consequently the permissions and approvals required
  - Helps you to meet regulatory and governance requirements
  - Retains familiar aspects of the NRES form system
• **IRAS** captures the information needed for the relevant approvals from the following review bodies:
  
  - Administration of Radioactive Substances Advisory Committee (ARSAC)
  - Gene Therapy Advisory Committee (GTAC)
  - Medicines and Healthcare products Regulatory Agency (MHRA)
  - Ministry of Justice
  - NHS / HSC R&D offices
  - NRES/ NHS / HSC Research Ethics Committees
  - National Information Governance Board (NIGB)
  - Social Care Research Ethics Committee

**Clinical Trial R&D Approvals (NIHR CSP)**

• **NIHR CSP**: NIHR Coordinated System for gaining NHS Permission
  
  - The National Institute for Health Research (NIHR) Coordinated System for gaining NHS Permission (CSP) ensures all quality assurance and statutory requirements in respect of clinical research are met, through standardising and streamlining the process for gaining NHS Permission in England. This will reduce both approval times and bureaucracy.

**NIHR Involvement in the Clinical Trial Process**

In 2006, the Department of Health set up the National Institute for Health Research to create a world-class health system within the NHS, with the Clinical Research Network as part of this wider organization ([NIHR CRN CC – About Us](#)).

At the centre of what we do is the Portfolio – a collection of high-quality clinical studies that benefit from the infrastructure provided by the Clinical Research Network. Many of these studies are Randomized Controlled Trials - considered by many in the medical profession to be the most robust form of clinical trial - although we also support other types of well-designed research ([NIHR CRN CC – About Us](#)).

This is how, in practice, we provide an "infrastructure" to support our Portfolio studies:
We run the coordinated system for gaining NHS permission (CSP) - a system through which researchers can apply for permission to run a clinical study in the NHS. We are constantly working to speed up and simplify this process, so that researchers can get a clinical study up and running quickly, with the minimum of bureaucracy.

We fund research support posts in the NHS, and provide training, so that researchers have access to experienced "front-line" staff, who can carry out the additional practical activities required by their study such as obtaining patient consent for participation, carrying out extra tests, and collecting the clinical data required for the research.

We provide funding to meet the costs of using facilities such as scanners and x-rays that are needed in the course of the study, so that research activity adds value to patient care, and doesn't drain NHS resources.

And we provide practical help in identifying and recruiting patients onto Portfolio studies, so that researchers can be confident of completing the study on time, and on target.

Although the Clinical Research Network operates as one organisation, we are made up of a number of different parts:

- Six “Topic” Research Networks (covering Cancer, Dementia and Neurodegenerative Diseases, Diabetes, Medicines for Children, Mental Health and Stroke)
- A Primary Care Research Network to support research in this part of the health service
- A Comprehensive Clinical Research Network, which covers all other disease areas.

The final element of the Clinical Research Network is the Coordinating Centre, which is responsible for managing the overall performance of the Networks. In addition to this, the Coordinating Centre team develops and delivers streamlined central systems (CSP), and undertakes specialist cross-cutting activities to support the commercial life-sciences industry, develop the research workforce, and promote patient and public involvement in clinical trials (NIHR CRN CC – About Us).

MHRA Inspection Findings: Ethical Approval
Source: Summary of MHRA GCP Inspection Findings 2006 - 2007
  - Lack of approval for study advertising – especially websites
  - Study conduct at sites outside of those in the application
  - Failure to notify sites for site-specific assessment exemption
  - Use of documents which are not those which received a favourable opinion or untimely re-consent where documents are revised
  - Ambiguity in what did receive a favourable opinion for example through typographical errors/omissions in the correspondence

Clinical Trial Responsibilities: The Sponsor

Definition: Sponsor

- Any individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial (As per Section 1.53 of ICH E6).
- “sponsor” means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial (As per Regulation 3.1 of SI 2004/1031).

  - Note – The definition of the “Sponsor of a Clinical Trial” is more detailed than provided for here. The reader is therefore strongly encouraged to read all of Regulation 3.

Clinical Trial Responsibilities: The Sponsor

- ICH E6: Guidelines for Good Clinical Practice
  - Refer to specifically to:
    - Section 5: The Sponsor’s Responsibilities
      - Section 5.1: Quality Assurance and Quality Control
      - Section 5.2: Contract Research Organisation (CRO)
• **Section 5.3:** Medical Expertise

• **Section 5.4:** Trial Design

• **Section 5.5:** Trial Management, Data Handling, and Record Keeping

• **Section 5.6:** Investigator Selection

• **Section 5.7:** Allocation of Responsibilities

• **Section 5.8:** Compensation to Subjects and Investigators

• **Section 5.9:** Financing

• **Section 5.10:** Notification/Submission to Regulatory Authorities

• **Section 5.11:** Confirmation of Review by IRB/IEC

• **Section 5.12:** Information on Investigational Product(s)

• **Section 5.13:** Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

• **Section 5.14:** Supplying and Handling Investigational Product(s)

• **Section 5.15:** Record Access

• **Section 5.16:** Safety Information

• **Section 5.17:** Adverse Drug Reaction Reporting

• **Section 5.18:** Monitoring

• **Section 5.19:** Audit

• **Section 5.20:** Non-Compliance

• **Section 5.21:** Premature Termination or Suspension of a Trial

• **Section 5.22:** Clinical Trial/Study Reports
  
  o Refer also to [ICH E3](#) – Structure and Content of Clinical Study reports

• **Section 5.23:** Multicentre Trials
• The Medicines for Human Use (Clinical Trial) Regulations (SI 2004/1031) as amended by SI 2006/1928
  
  o Refer Specifically to:
    
    ▪ Regulation 3: Provides for a definition of the Sponsor of a clinical trial and details the accountability and responsibilities
    
    ▪ Regulation 3A: Sponsor’s Responsibility for the Investigator’s Brochure

**Clinical Trial Responsibilities: The Investigator**

**Definition: Chief Investigator**

- “chief investigator” means—

- (a) in relation to a clinical trial conducted at a single trial site, the investigator for that site, or

- (b) in relation to a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial (As per Regulation 2.1 of SI 2004/1031).

**Definition: Investigator**

- A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (As per Section 1.34 of ICH E6).

- ‘investigator’: a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator (As per Article 2(f) of 2001/20/EC)
"investigator" means, in relation to a clinical trial, the authorised health professional responsible for the conduct of that trial at a trial site, and if the trial is conducted by a team of authorised health professionals at a trial site, the investigator is the leader responsible for that team (As per Regulation 2.1 of SI 2004/1031).

Clinical Trial Responsibilities: The Investigator

- ICH E6: Guidelines for Good Clinical Practice
  - Refer to specifically to:
    - Section 4: The Investigator’s Responsibilities
      - Section 4.1: Investigator’s Qualifications and Agreements
      - Section 4.2: Adequate Resources
      - Section 4.3: Medical Care of Trial Subjects
      - Section 4.4: Communication with the Ethics Committee(s)
      - Section 4.5: Compliance with the Protocol
      - Section 4.6: Investigational Products
      - Section 4.7: Randomisation Procedures and Unblinding
      - Section 4.8: Informed Consent of Trial Subjects
      - Section 4.9: Records and Reports
      - Section 4.10: Progress Reports
      - Section 4.11: Safety Reporting
      - Section 4.12: Premature Termination or Suspension of a Trial
        - Refer also to Section 4.5 of ICH E9 (Statistical Principles for Clinical Trials)
      - Section 4.13: Final Report(s) by the Investigator

The Investigator’s Brochure (IB)
Definition: **Investigator’s Brochure**

- A Compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (As per Section 1.36 of [ICH E6](#)).

- ‘investigator’s brochure’: a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects (As per Article 2(g) of [2001/20/EC](#)).

- “investigator’s brochure” means a document containing a summary of the clinical and nonclinical data relating to an investigational medicinal product which are relevant to the study of the product in human subjects (As per Regulation 2.1 of [SI 2004/1031](#)).

**The Investigator’s Brochure (IB): General Guidance**

The Investigator’s Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational medicinal product (IMP) that are relevant to the study of the product in humans (as per Section 7.1 of [ICH E6](#)).

Its purpose is to provide the Investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures (as per Section 7.1 of [ICH E6](#)).

The IB also provides insight to support the clinical management of the study subjects during the course of a clinical trial (as per Section 7.1 of [ICH E6](#)).

The information SHOULD be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician, or potential Investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial (as per Section 7.1 of [ICH E6](#), Article 8 of [2005/28/EC](#) and Regulation 3A of [SI 2004/1031](#) as amended by [SI 2006/1928](#)).

The Investigator Brochure should be “validated and updated by the Sponsor at least once a year” (As per Article 8.3 of [2005/28/EC](#) and Regulation 3A(b) of [SI 2004/1031](#) as amended by [SI 2006/1928](#)).

- [ICH E6](#): Good Clinical Practice Guidelines
This is the only document that provides comprehensive guidance on the Investigator’s Brochure.

Refer to specifically to:

- **Section 7**: Investigator’s Brochure
  - **Section 7.1**: Introductions
  - **Section 7.2**: General Considerations
  - **Section 7.3**: Contents of the Investigator’s Brochure
  - **Section 7.4**: Appendix 1 – Example IB Title Page
  - **Section 7.5**: Appendix 2 – Example IB Table of Contents


Refer specifically to:

- **Article 8**: Investigator’s Brochure
  - 1. The information in the investigator’s brochure, referred to in Article 2(g) of Directive [2001/20/EC](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32001H0020&from=EN), shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial.
  - The first subparagraph shall apply also to any update of the investigator’s brochure.
  - 2. If the investigational medicinal product has a marketing authorisation, the **Summary of Product Characteristics** may be used instead of the investigator’s brochure.
  - 3. The investigator’s brochure shall be validated and updated by the sponsor at least once a year.


  Refer Specifically to:
• **Regulation 3A**: Sponsor’s Responsibility for the Investigator’s Brochure

• **Regulation 15.5.e**: Documents Submitted to the Ethics Committee

• **Schedule 3, Part 1.3.b**: Particulars and Documents That Must Accompany an Application for an Ethics Committee Opinion, a Request for Authorisation, a Notice of Amendment and a Notification of the Conclusion of a Trial

  • Provides for the use of an Investigator’s Brochure for the proposed trial or, where the investigational medicinal product has a marketing authorisation and the product is to be used in accordance with the terms of that authorisation, the use of the summary of product characteristics relating to that product.

• CHCUK Website: [GCP Considerations – The Investigator’s Brochure (Mar 2011)](http://www.chcuk.org.uk/GCP/considerations_IB_SmPC.pdf)

  o Questions are often raised by clinical study team members regarding the use of an Investigator’s Brochure (IB), an IB supplemented by a Summary of Product Characteristics (SmPC), or an SmPC to support products that are already registered. This requires further elaboration and discussion in order to provide meaningful and specific guidance.

  o This short report was produced in response to such questions and provides Guidance on the purpose, design and management of an Investigator’s Brochure (IB) with particular emphasis on the UK requirements.

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### The Study Protocol

**Definition: Protocol**

- A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol reference documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments (As per Section 1.44 of ICH E6).

- ‘protocol’: a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the
protocol, successive versions of the protocol and protocol amendments (As per Article 2(h) of 2001/20/EC).

- “protocol” means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial (As per Regulation 2.1 of SI 2004/1031).

General Guidance on the Structure and Content of a Protocol

An important initial reference point for anyone looking to develop a clinical trial protocol is Section 6 of ICH E6, which provides guidance on the structure and content of the clinical trial protocol.

- ICH E6: Guidelines for Good Clinical Practice
  - Refer to specifically to:
    - **Section 6**: Clinical Trial Protocol and Protocol Amendments
      - **Section 6.1**: General Information
      - **Section 6.2**: Background Information
      - **Section 6.3**: Trial Objectives and Purpose
      - **Section 6.4**: Trial Design
      - **Section 6.5**: Selection and Withdrawal of Subjects
      - **Section 6.6**: Treatment of Subjects
      - **Section 6.7**: Assessment of Efficacy
      - **Section 6.8**: Assessment of Safety
      - **Section 6.9**: Statistics
      - **Section 6.10**: Direct Access to Source Data/Documents
      - **Section 6.11**: Quality Control and Quality Assurance
      - **Section 6.12**: Ethics
      - **Section 6.13**: Data Handling and Record Keeping
• Section 6.14: Financing and Insurance

• Section 6.15: Publication Policy

• Section 6.16: Supplements

• ICH E8: General Considerations for Clinical Trials
  o This efficacy guideline provides a useful oversight to, and guidance on, the considerations for individual clinical trials such as:
    ▪ Trial types and phases
    ▪ Objectives, design, conduct and analysis of results.

Clinical Trial Insurance

Definition: Insurance or Indemnity

• “Insurance or indemnity” includes provision for meeting losses or liabilities—

(a) under a scheme established under—

(i) section 21 of the National Health Service and Community Care Act 1990 (schemes for meeting losses and liabilities etc. of certain health service bodies in England and Wales),

(ii) section 85B of the National Health Service (Scotland) Act 1978 (schemes for meeting losses and liabilities etc. of certain health service bodies in Scotland), or

(iii) Article 24 of the Health and Personal Social Services (Northern Ireland) Order 1991 (schemes for meeting losses and liabilities etc. of certain health service bodies in Northern Ireland), or

(b) in accordance with guidance issued by—

(i) the Secretary of State,

(ii) the Scottish Ministers,

(iii) the National Assembly for Wales, or
The Requirement for Insurance in Clinical Trials

According to the Clinical Trials Directive (2001/20/EC), in preparing its opinion, the Ethics Committee shall consider, in particular:

- Provision for indemnity or compensation in the event of injury or death attributable to a clinical trial (As per Article 6.3(h) of 2001/20/EC).
- Any insurance or indemnity to cover the liability of the investigator and sponsor (As per Article 6.3(i) of 2001/20/EC).

As transposed into UK law through Regulation 15(5) and Part 1.1(g) of Schedule 3 of SI 2004/1031.

Insurance Due Diligence

There is much talk nowadays about the need to perform ‘insurance due diligence’. What is meant by this? In essence, we know that there is a legal requirement to ensure that the Sponsor has an insurance policy (indemnity or compensation) in place in the event of injury to, or even death of, a trial subject, which is attributable to the trial.

We have proof of this cover in the form of an insurance certificate. However, the MHRA have quite rightly pointed out that there needs to be a review of the insurance policy to ensure that all of the trial subject population is covered by the policy, or re-phrased that none of the trial population is excluded from the cover of the policy. Refer especially to the ‘exemptions’ section of the insurance policy. This is a simple step that must be performed as part of a Sponsor’s duty of care and the fact that it has been done should be documented (if it isn’t written down it never happened).

MHRA GCP Inspection Findings: Insurance
Source: Summary of MHRA GCP Inspection Findings 2006 - 2007

- Insurance policy terms and conditions with exemptions; for example certain patient populations, in absence of compliance with protocol etc – very common that these terms & conditions are NOT reviewed by the organisation purchasing the cover or to whom cover is extended

MHRA GCP Inspection Findings: Insurance Issues in the TGN1412 Study

Parexel (a contract research organisation) was contracted by the sponsor, TeGenero AG, to conduct an entry into human study of the monoclonal antibody TGN1412. Eight healthy male volunteers were recruited and dosed by Parexel Clinical Pharmacology Research Unit (CPRU) on 13th March 2006. On the same day Serious Adverse Events (SAEs) were reported in 6 of the 8 subjects (Expert Scientific Group on Phase One Clinical Trials, Final Report, 30th November 2006).

According to Parexel CPRU, the subjects experienced “Cytokine Release Syndrome”, which was reported as “Life-Threatening”. The drug codes were broken by Parexel, this confirmed that the 6 subjects who experienced SAEs received active drug and the two subjects who did not experience adverse events received placebo (Expert Scientific Group on Phase One Clinical Trials, Final Report, 30th November 2006).

Inspections were subsequently performed by the MHRA and other European authorities and the testing performed on samples following the incident (Expert Scientific Group on Phase One Clinical Trials, Final Report, 30th November 2006).

The objective of this investigation was to determine whether there were any errors in the conduct of this trial which might have caused the serious adverse events (Expert Scientific Group on Phase One Clinical Trials, Final Report, 30th November 2006).

The inspectors reported that there were no findings which were believed to be likely to have contributed to the Serious Adverse Events experienced by the trial subjects who received the study drug. However, as a result of the GCP inspection, a number of discrepancies were identified which included insurance issues. According to the MHRA GCP Inspection report:

- Parexel had a duty to review TeGenero’s insurance policy to ensure that one was in place and that there were no exclusion categories within it that might impact upon their volunteers, in this study. They failed to do this although no such exclusions were subsequently found.
Further Information about this particular trial can be found at:

- [MHRA Press Release on the TGN1412 Incident and Related Documentation](#) (April 2006)
  - [TGN1412 Clinical Trial Application: Release of Information Cover Note](#)
  - [TGN1412 Clinical Trial: Investigational Medicinal Product Dossier](#)
  - [TGN1412 Clinical Trial: Assessment Report](#)
  - [TGN1412 Clinical Trial: Investigator's Brochure](#)
  - [TGN1412 Clinical Trial: Protocol](#)
  - [Investigations into Adverse Incidents During Clinical Trials of TGN1412: Interim Report](#)
  - [Latest Findings on Clinical Trial Suspension: Press Release](#)

### Essential Documents, the Trial Master File (TMF) & Archiving

In the UK, the regulatory requirements applicable to Trial Master File (TMF) management and archiving are listed in Article 31A and Schedule 1 of the Medicines for Human Use (Clinical Trials) Regulations 2004 ([SI 2004/1031](#)) as amended by [SI 2006/1928](#), with further guidance provided in the [MHRA Guidance on Archiving (2006)](#).

### Definitions

**Definition: Essential Documents**

- Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (As per Section 1.23 of [ICH E6](#)).
  - Refer also to Section 8 of [ICH E6](#) – Essential Documents for the Conduct of a Clinical Trial
Definition: **Source Data**

- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (As per Section 1.51 of ICH E6).

Definition: **Source Documents**

- Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial) (As per Section 1.52 of ICH E6).

The Trial Master File (TMF) and Archiving: An Overview

According to Section 2 of the European Commission’s document entitled ‘Recommendation on the Content of the Trial Master File and Archiving (July 2006)’:

The trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated according to Article 16 of Directive 2005/28/EC.

The essential documents should be filed in an organised way that will facilitate management of the clinical trial, audit and inspection (Sponsor Trial Master File and Investigator and other trial Site Files).

According to Article 17, third paragraph, of Directive 2005/28/EC essential documents should be retained securely prior to archive and then archived for sufficient periods to allow for audit and inspection by regulatory authorities and should be readily available upon request.

Applicable Regulations and Guidelines
• **ICH E6**: Good Clinical Practice Guidelines
  
  o Refer to specifically to:

    ▪ **Section 8**: Essential Documents for the Conduct of a Clinical Trial
      
      • Provides detailed guidance on essential documents and the filing requirements for the clinical trial sponsor (Trial Master File or ‘TMF’) and investigator (Investigator site file or ‘ISF’). Although the collective of all the clinical trial documents (i.e., those stored with both the trial Sponsor and Investigator) is the Trial Master File, the file of the Sponsor is commonly referred to as the ‘Trial master File’ and that of the Investigator(s) as the ‘Investigator Site File’.

    ▪ **Section 4.9**: Describes the Investigator’s Responsibilities with Regards to Maintaining and Retaining Clinical Trial Documents.

  
  o According to Article 15.5:

    ▪ “The detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with this Directive shall be adopted and revised in accordance with the procedure referred to in Article 21(2)”.

• **2005/28/EC (The GCP Directive)**: Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
  
  o Refer specifically to Chapter 4 which implements the detailed guideline of the Master File in the trial and archiving, and states that the Commission shall publish additional guidance in order to specify the content of these documents.
• European Commission Recommendation on the Content of the Trial Master File and Archiving (July 2006)

  
  o This document is a consolidated version of Directive 2001/83/EC and the following 7 amendments to the Directive†:

  
    
    • Amends Annex I of 2001/83/EC ‘Analytical, Pharmacotoxicological and Clinical Standards and Protocols in Respect of the Testing of Medicinal Products’

  
  
  

    
    o Refer specifically to Section 5.2(c) of Annex I of the Marketed Products Directive (2001/83/EC as amended)

• SI 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations
  
  o As amended by SI 2006/1928
  
  o Refer Specifically to:

† The reader is urged to regularly check the list of amendments to Directive 2001/83/EC, which are listed in Eudralex Volume 1 to ensure that they are aware of all the current amendments. Note that this current consolidated version of Directive 2001/83/EC does not include all of the amendments, such as 2009/53/EC.
Regulation 31A: Trial Master File and Archiving

  - Although written primarily with archiving of GLP documents in mind this is still a very relevant guide and resource for archiving of GCP-related documents

NHS Guidance on Retention of Clinical Trial Records

- Department of Health Guidance: Research involving the NHS - Retention of Records (2007)

Document Retention Timeframes and Requirements

There can be some confusion with respect to how long essential documents should be retained after the completion of a clinical trial. Article 17 of the GCP Directive (2005/28/EC) states that, “the Sponsor and Investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion.”

However, according to Section 5.2(c) of Annex I of the Marketed Products Directive (2001/83/EC as amended):

Marketing Authorisation Holders must arrange for clinical trial documents (including case report forms) other than subject’s medical files, to be kept by the owners of the data:

- For at least 15 years after completion or discontinuation of the trials;
- Or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community;
- Or for at least two years after the formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.
The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

Therefore, it is best practice to assume that all essential documents (as contained in the Sponsors TMF and the Investigator’s Site File) are to be retained for at least 15 years and, in any case, until otherwise notified by the study Sponsor.

The Regulatory Green Light (RGL)

The Regulatory Green Light (RGL) is an important control mechanism, which helps to ensure that the experimental drug or ‘Investigational Medicinal Product’ isn’t released to the clinical trial site until all of the approvals are in place, and therefore all of the regulatory requirements have been met. The last thing we want to do is release a drug before we know that it meets the strict safety requirements put in place to protect the trial participants.

The Regulatory Green Light (RGL) is therefore a process, which is implemented by study Sponsors to ensure that the IMP is not released until all of the required approvals are in
place. This will vary from country to country and often includes not only the Competent Authority and Ethics Committee approvals but also the Hospital Trust approvals, and any other pertinent bodies, such as ARSAC in the UK.

**Definition: Investigational Medicinal Product (IMP)**

- A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (As per Section 1.33 of ICH E6).

- ‘Investigational medicinal product’: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (as per Article 2(d) of 2001/20/EC).

- “investigational medicinal product” means a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial—
  - used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization,
  - used for an indication not included in the summary of product characteristics under the authorization for that product, or
  - used to gain further information about the form of that product as authorised under the authorization (As per Regulation 2(1) of SI 2004/1031).

**Definition: Good Manufacturing Practice (GMP)**

- Good manufacturing practice means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use (As per Article 2.6 of 2003/94/EC).
The application of GMP to the manufacture of IMPs is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture (As per the ‘Principle’ Section of Annex 13).

IMPs should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol (As per Section 2.12 of ICH E6).

Definition: The Regulatory Green Light (RGL)

- Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step release procedure: certification by the Qualified Person; and release following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. The sponsor should ensure that these are consistent with the details actually considered by the Qualified Person. Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor (As per Paragraph 44 of Annex 13).

The Regulatory Green Light (RGL) Process

The Regulatory Green Light (RGL) Process is a 2-step release process, as described in Paragraph 44 of Annex 13.

1. Certification by the Qualified Person (QP)
   a. Refer Specifically to:
      i. Article 13(3) of 2001/20/EC
      ii. Regulation 43(2) of SI 2004/1031
   b. The QP certifies that each Batch of IMP has been manufactured in accordance with:
      i. Standards of GMP (2003/94/EC)
      ii. The Product Specification File (Paragraph 9, Annex 13)
      iii. The Information Notified to the MHRA (As per Article 9.2 of 2001/20/EC & Regulation 43(2) of SI 2004/1031)
2. **Release of IMP to the trial site following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of the Clinical Trials Directive** *(2001/20/EC)*

a. Refer Specifically to:

i. Article 9 of *2001/20/EC*

   1. The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.

ii. Regulation 12 of *SI 2004/1031*

b. Before starting a clinical trial the sponsor must ensure that all of the relevant approvals have been granted (Section 5.14.2, *ICH E6*)

   i. Competent authority approval (Article 9.2 of *2001/20/EC* and Regulation 12(3) of *SI 2004/1031*)

   ii. Ethics Committee favourable opinion (Article 9.1, *2001/20/EC* and Regulation 12(3) of *SI 2004/1031*)

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**MHRA GCP Inspection Findings: Investigational Medicinal Product (IMP)**

- **Source:** *Summary of MHRA GCP Inspection Findings 2006 - 2007*
  - Missing documentation – no records/partial records to confirm who got what, when
  - Supplies which do not have documentation to confirm UK/European requirements for quality and compliance with the trial authorisation(s) – failing or missing ‘green light’ process bringing management approval (insurance/indemnity), ethical and regulatory approval together
  - Emergency codes not supplied concurrent with the trial medication or prior to the study start

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**MHRA GCP Inspection Findings: Regulatory Green Light Issues (RGL)**

- **Source:** MHRA Conference Oct 2006 (Evolution of GCP inspection – From Process to Compliance)
It is required that there is a 2 step process for release of IMP (QP certification against the product specification file) and “regulatory green light” (eg release against all required approvals etc). MHRA expect to see documented evidence of the RGL release prior to shipment.

**Specific Example:** There was evidence that the regulatory green light (RGL) process for IMP was not robust. Whilst a checklist of essential documents was prepared and signed off by clinical operations and QA, this was not linked to the ability to order the IMP release from the contractor/sponsor to the investigator site, as this could be done independently by the Project Manager. For example, for study 2, the instructions to ship to investigator site was made on 06 Mar 06, but the checklist of essential documents was not approved by QA until the 07 Mar 06, the day the IMP was received at the investigator site.

**Historical Background Information:** The 1937 Sulfanilamide Disaster (United States Example)

- **Sulfanilamide Disaster:** Taste of Raspberries, Taste of Death - The 1937 Elixir Sulfanilamide Incident by Carol Ballentine

- **Example from the USA:** By the 1930s it was widely recognized that the Food and Drugs Act of 1906 was obsolete, but bitter disagreement arose as to what should replace it. By 1937 most of the arguments had been resolved but Congressional action was stalled. Then came a shocking development—the deaths of more than 100 people after using a drug that was clearly unsafe. The incident hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products.

**Clinical Trial Registration**

**Clinical Trial Registration:** Joint Position on the Disclosure of Trial Information
In accordance with the Joint Position Paper on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases‡ which was updated on the 10th November 2009:

**What Should be Registered?**

All clinical trials§ in patients conducted on a medicinal product at a minimum should be submitted for listing.

In all cases disclosure will be undertaken in a manner consistent with applicable national laws and rules governing protection of intellectual property.

**When Should the Information be Posted?**

No later than 21 days after the initiation of patient enrollment, without prejudice to national legal requirements.

**Where Should this Information be Posted?**

Registration of clinical trials on any one of a number of free, publicly accessible, internet-based registries should achieve the intended objectives.

Company clinical trial registries as well as registries such as the National Library of Medicine in the USA (www.clinicaltrials.gov), the UK Current Controlled Trials (www.controlled-trials.com) and the Japan Pharmaceutical Information Center (www.clinicaltrials.jp) can be used for this purpose, regardless of where the trial is conducted.

**Clinical Trial Registers: ClinicalTrials.gov**

- ClinicalTrials.gov
  - ClinicalTrials.gov: Factsheet
- ClinicalTrials.gov Results Database
  - Results Reporting Requirements Under U.S. Federal Law
  - **Scope:** While results information may be submitted for any registered study, US Public Law 110-85 (Food and Drug Administration Amendments Act of

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‡ The Joint Position sets forth the views of the innovative pharmaceutical industry, as represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA).

§ For purposes of this Position, a « clinical trial » means an interventional trial involving human subjects from Phase 1 and beyond. For example, the term does not include the use of a medicinal product in the normal course of medical practice or non-clinical laboratory studies.
2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the study sponsor or designated principal investigator) register and report results of certain "applicable clinical trials" that were initiated or ongoing as of September 27, 2007:

- **Trials of Drugs and Biologics**: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation.

- **Trials of Devices**: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

- "**Applicable clinical trials**" generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE).

- **Timing**: In general, a responsible party is required to submit "basic results" information not later than one year after the "primary completion date" or date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated (Note that, if submitted by the data provider, the "primary completion date" is listed in the study protocol record).

**Clinical Trial Registers: IFPMA Clinical Trials Portal**

- [IFPMA ClinicalTrials Portal](http://www.ifpma.org/clinicaltrials)

  o The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) facilitates transparency and easier access to clinical trial information through a search portal that links to online information on industry-sponsored clinical trials, which exists in a number of registries and databases. The IFPMA Clinical Trial Portal ([www.ifpma.org/clinicaltrials](http://www.ifpma.org/clinicaltrials)) was launched in September 2005.

  o The IFPMA Clinical Trial Portal helps patients, physicians and other stakeholders to access information about ongoing trials as well as the outcome of trials as it searches established clinical trials registries and results databases.
Clinical Trial Registers: Current Controlled Trials

- Current Controlled Trials
  - Current Controlled Trials allows users to search, register and share information about randomised controlled trials. Access to all the information on this site is free; charges for the registration services offered by Current Controlled Trials are available on request. Publication services are also available via the range of open access peer-reviewed journals published by the sister company, BioMed Central.

Clinical Trial Registers: Japan Pharmaceutical Information Center (JAPIC)

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information
The Process of Informed Consent

The NIHR CRN Workforce Development website provides an Informed Consent Resources toolkit which includes articles, references, signposting and other useful links.

Definitions

Informed Consent Definition: The Nuremburg Code

The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility, which may not be delegated to another with impunity (as per Paragraph 1 of the Nuremburg Code, 1947).

Informed Consent Definition: The Declaration of Helsinki (1996)

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing (Declaration of Helsinki, Section 1.9).

Informed Consent Definition: ICH E6
A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form (ICH E6, Section 1.28).


Decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional circumstances, as provided for in national legislation (2001/20/EC, Article 2(j)).

Informed Consent Definition: The Medicines for Human Use (Clinical Trials) Regulation 2004

A person gives informed consent to take part, or that a subject is to take part, in a clinical trial only if his decision —

(a) is given freely after that person is informed of the nature, significance, implications and risks of the trial; and

(b) either—

(i) is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or

(ii) if the person is unable to sign or to mark a document so as to indicate his consent, is given orally in the presence of at least one witness and recorded in writing.

(As per Part 1 of Schedule of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031))

Informed Consent: General Considerations

- CHCUK Website: GCP Considerations – Informed Consent (March 2011)
Informed consent is the key foundation of Good Clinical Practice and yet we still regularly see failings in this area as evidenced through audit and inspection findings. The hope is that by further educating clinical researchers we can reduce these failings and increase the rigour with which we conduct clinical trials. Ultimately, our goal is always to ensure that the rights, safety and welfare of the trial subject are respected and protected. In human terms, you should ask yourself if you would do anything differently if it was your son, daughter, wife, husband, mother or father who was sitting before you during the informed consent discussion.

This short report provides an overview of the recent history, which led to the drafting of the regulations as we know them today, as well as, providing a practical overview of the applicable UK regulatory framework.

- The Medicines for Human Use (Clinical Trial) Regulations (SI 2004/1031)
  - Refer Specifically to:
    - **Schedule 1, Part 3**: Provides a Definition of Informed Consent
    - **Schedule 1, Part 3**: Conditions Which Apply to an Adult Able to Consent or Who Has Given Consent Prior to the Onset of Incapacity

- The National Research Ethics Service (NRES) website: Contains useful documentation and guidance on informed consent:
    - Provides guidance and templates for patient information leaflets (PILs) and informed consent forms (ICFs)
    - Summarises the statutory requirements for informed consent of participants in clinical trials of investigational medicinal products (CTIMPs). The requirements are set out in Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164, and SI 2010/1882
    - Refer specifically to:
      - **Paragraphs 8 to 9**: Definition of Informed Consent
• **Paragraphs 10 to 12**: Conditions that Apply to the Giving of Informed Consent by a Capable Adult
  
  o NRES Information Paper on Informed Consent in Clinical Trials of Investigational Medicinal Products v3 May 2008
  
  o Making written information easier to understand for people with learning disabilities: Guidance for people who commission or produce Easy Read information – Revised Edition 2010.


• The NIHR CRN Workforce Development Website: Informed Consent Resources toolkit
  
  o Includes articles, references, signposting and other useful links.

• The Clinical Trials Directive (2001/20/EC)
  
  o Refer specifically to:
    
    ▪ **Article 3**: Protection of Clinical Trial Subjects

• ICH E6: The Basic Building Blocks of Informed Consent
  
  o Refer to Section 4.8 of ICH E6 for the common basic building blocks of the Informed Consent Form (ICF), as well as the general considerations for the informed consent process itself.

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**Informed Consent: Guidance on ‘Time to Consent’**

A question that is commonly encountered when considering the informed consent process is “how long should I allow for the subject to read and consider the information before inviting them to consent”?

NRES have provided the following guidance to aid researchers:

• **Time to Consent**: Consent must be informed, voluntary and time given to consideration to participate needs to be thought through on a case-by-case basis.

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**Informed Consent: Involving Public and Patients in Research**
• **NRES Guidance on PILs & ICFs**: The National Research Ethics Service (NRES) Guidance for Researchers & Reviewers on Information Sheets & Consent Forms, May 2009
  
  - Provides guidance and templates for patient information leaflets (PILs) and informed consent forms (ICFs)
  - Refer specifically to:
    - **Section 3.0**: Involving Public and Patients and Research
    - **Annex 7**: Involving Patient Groups
      - It is good practice, may improve trial relevance, design and recruitment if researchers involve patient groups. Such studies are more likely to receive a favourable opinion. It will indicate an ethical, patient-centred approach.

• **INVOLVE Website**
  - INVOLVE is a national advisory group, funded by the National Institute for Health Research (NIHR). Its role is to support and promote active public involvement in NHS, public health and social care research.
  - [INVOLVE: Good Practice in Active Public Involvement in Research](#)

**Informed Consent: The Participants Perspective**

• **Healthtalkonline Website**
  - Healthtalkonline is the award-winning website of the DIPEX charity and replaces the website formerly at dipex.org. Healthtalkonline lets you share in other people's experiences of health and illness. You can watch or listen to videos of the interviews, read about people's experiences and find reliable information about conditions, treatment choices and support.
  - The information on Healthtalkonline is based on qualitative research into patient experiences, led by experts at the University of Oxford. These personal stories of health and illness will enable patients, families and healthcare professionals to benefit from the experiences of others.
  - Peoples Stories
Informed Consent: Minors

- The Medicines for Human Use (Clinical Trial) Regulations (SI 2004/1031)
  - Refer Specifically to:
    - **Schedule 1, Part 3**: Provides a Definition of Informed Consent
    - **Schedule 1, Part 4**: Conditions and Principles Which Apply in Relation to a Minor
  - As amended by The Medicines for Human Use (Clinical Trial) and Blood Safety and Quality (Amendment) Regulations 2008 (SI 2008/941)
    - Amends Schedule 1, Part 1 of SI 2004/1031 to allow minors into a clinical trial without the prior consent of their legal representative assuming certain conditions are met (Emergency Consent)
    - Implements Section 4.8.15 of ICH E6
  - Provides guidance and templates for patient information leaflets (PILs) and informed consent forms (ICFs)
  - Refer specifically to:
    - **Section 7.0**: Guidance for Design of Information Sheets for Children/Young People
    - **Annex 11**: Children’s Research - What are Acceptable Risks?
    - **Annex 12**: Children’s Research – Children’s Views
    - **Annex 13**: Children’s Research - When Should the Child’s Consent be Sought?
    - **Annex 14**: Children, Research and Potential Pregnancy
    - **Annex 15**: Children’s Research - The Principles
    - **Annex 16**: Children’s Research – The Need
- **NRES Information Paper on Informed Consent in Clinical Trials (2008)**
o Summarises the statutory requirements for informed consent of participants in clinical trials of investigational medicinal products (CTIMPs). The requirements are set out in Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164 and SI 2010/1882

o Refer specifically to:

  ▪ **Paragraphs 13 to 15:** General Considerations and Hierarchy of Consent in Minors
  ▪ **Paragraphs 16 to 17:** Emergency Situations
  ▪ **Paragraph 18:** Conditions and Principles Applying to Minors
  ▪ **Table 1:** Hierarchy of Informed Consent for a Minor
  ▪ **Annex A:** Conditions and Principles Which Apply to the Inclusion of a Minor in a Clinical Trial

• **The UK’s Medicines for Children Research Network (MCRN)**
  o **MCRN Guidance Notes for Involving Children and Young People in Research (2007)**
    ▪ Refer Specifically to:
      ▪ **Section 4:** Gaining Consent

• The NIHR CRN Workforce Development Website: Informed Consent Resources toolkit
  o Includes articles, references, signposting and other useful links.

  o Refer specifically to:
    ▪ **BOX A:** Protecting Research Participants’ Rights (Pages 10 – 12)
      ▪ Provides a helpful scenario of a parent and child’s perspective of clinical trials and informed consent
  
  o Applicable to research conducted in Scotland
  
  o Refer specifically to:
    
    ▪ **Paragraph 2.6**: Standards
      
      • The Scottish Executive Health Department requires that all health research involving patients, service users, care professionals or volunteers, or their organs, tissue or data, is reviewed independently to ensure it meets ethical standards. Informed consent is at the heart of ethical research. Most studies involving individuals must have appropriate arrangements for obtaining consent and the NHS ethics review process pays particular attention to those arrangements. The law gives special protection to people who are unable to give consent on their own behalf. For example, *The Adults with Incapacity (Scotland) Act 2000* provides safeguards for adults who lack capacity to consent to research. Care is needed when seeking consent from children and from vulnerable adults, such as those with mental health problems or learning difficulties. Arrangements must be made to ensure that relevant information is provided in appropriate written or pictorial form and that the role and responsibilities of parents, carers or supporters are clearly explained and understood.

• The Clinical Trials Directive (*2001/20/EC*)
  
  o Refer specifically to:
    
    ▪ **Article 4**: Clinical Trials on Minors

• European Commission Guidance Document: *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (2008)*
  
  o Refer specifically to:
    
    ▪ **Section 5.7**: Assent
    
    ▪ **Section 6.0**: The Process of Informed Consent
    
    ▪ **Section 7.0**: Assent from Children
Annex 3: Information for Informed Consent

- ICH E11: Clinical Investigation of Medicinal Products in the Paediatric Population

Informed Consent: Incapacitated Adults

- The Medicines for Human Use (Clinical Trial) Regulations (SI 2004/1031)
  - Refer Specifically to:
    - Schedule 1, Part 3: Provides a Definition of Informed Consent
    - Schedule 1, Part 5: Conditions and Principles Which Apply in Relation to An Incapacitated Adult
  - As amended by The Medicines for Human Use (Clinical Trial) Amendment Regulations (No.2) 2006 (SI 2006/2984)
    - Amends Schedule 1, Part 1 of SI 2004/1031 to allow incapacitated adults into a clinical trial without the prior consent of their legal representative assuming certain conditions are met (Emergency Consent)
    - Implements Section 4.8.15 of ICH E6

  - Provides guidance and templates for patient information leaflets (PILs) and informed consent forms (ICFs)
  - Refer specifically to:
    - Section 8.0: Information Sheets for Adults Without Capacity
    - Annex 29: Capacity or Competence - How Should They be Assessed?

  - Summarises the statutory requirements for informed consent of participants in clinical trials of investigational medicinal products (CTIMPs). The requirements are set out in Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164, and SI 2010/1882
Refer specifically to:

- **Paragraph 19**: Definition of an Incapacitated Adult
- **Paragraph 20**: Hierarchy of Consent
- **Paragraph 21 – 22**: Emergency Consent
- **Paragraphs 23**: Conditions and Principles Applying to Incapacitated Adults
- **Table 2**: Hierarchy of Informed Consent for an Incapacitated Adult
- **Annex B**: Conditions and Principles Which Apply to the Inclusion of an Incapacitated Adult in a Clinical Trial


  o Refer specifically to:
    - **Section 12**: Research Involving Adults Unable to Consent for Themselves
      - **Section 12.11 to 12.65**: Research Other than CTIMPs
        o Sections 30-34 of the *Mental Capacity Act* make detailed provision relating to research involving adults aged 16 or over who are unable to consent for themselves. *The Act* applies in England and Wales only. It has no application to CTIMPs.
        o The application of these provisions is not limited to medical and biomedical research, health-related research or research taking place within the NHS. It applies potentially to research in the context of social care and in any other context where participants could lack capacity to give informed consent.


  o Applicable to research conducted in Scotland
  o Refer specifically to:
Paragraph 2.6: Standards

- The Scottish Executive Health Department requires that all health research involving patients, service users, care professionals or volunteers, or their organs, tissue or data, is reviewed independently to ensure it meets ethical standards. Informed consent is at the heart of ethical research. Most studies involving individuals must have appropriate arrangements for obtaining consent and the NHS ethics review process pays particular attention to those arrangements. The law gives special protection to people who are unable to give consent on their own behalf. For example, *The Adults with Incapacity (Scotland) Act 2000* provides safeguards for adults who lack capacity to consent to research. Care is needed when seeking consent from children and from vulnerable adults, such as those with mental health problems or learning difficulties. Arrangements must be made to ensure that relevant information is provided in appropriate written or pictorial form and that the role and responsibilities of parents, carers or supporters are clearly explained and understood.

- The NIHR CRN Workforce Development Website: [Informed Consent Resources](#) toolkit
  - Includes articles, references, signposting and other useful links.

- The Clinical Trials Directive ([2001/20/EC](#))
  - Refer specifically to:
    - **Article 5**: Clinical Trials on Incapacitated Adults Not Able to Give Informed Legal Consent

- [The Mental Capacity Act 2005](#)
  - Applicable to trial subjects in England & Wales
    - Explanatory Notes: Mental Capacity Act (2005)
    - Code of Practice: Mental Capacity Act 2005
  - The reader is urged to consider not only the Act (Primary Legislation) but also the relevant Statutory Instruments (Secondary Legislation), whether they be
Rules, Regulations or Orders, which may contain relevant information not detailed in the Act itself (see below):


- Department of Health Resource: [Mental Capacity Act 2005 - Summary](#)
- **The Adults with Incapacity (Scotland) Act 2000**
  - Applicable to trial subjects in Scotland
  - The reader is urged to consider not only the Act (Primary Legislation) but also the relevant Statutory Instruments (Secondary Legislation), whether they be Rules, Regulations or Orders, which may contain relevant information not detailed in the Act itself (see below):
    - **SSI 2002/190** (Scotland): [Adults with Incapacity (Ethics Committee) (Scotland) Regulations 2002](#)

**MHRA GCP Inspection Findings**

Informed consent is the key foundation of Good Clinical Practice and yet we still regularly see failings in this area as evidenced through audit and inspection findings. The hope is that by further educating clinical researchers we can reduce these failings and increase the rigour with which we conduct clinical trials. Ultimately, our goal is always to ensure that the rights, safety and welfare of the trial subject are respected and protected. In human terms, you should ask yourself if you would do anything differently if it was your son, daughter, wife, husband, mother or father who was sitting before you during the informed consent discussion.

It is sometimes helpful to understand what is required by looking at what is considered a non-compliance. Hence, the information provided below.

**MHRA GCP Inspection Findings: Informed Consent**


**No Records of Consent Being Taken**
It has been observed during inspection at investigator sites where consent was not taken
prior to study procedures being conducted

**Missing Elements**

It is expected that all elements are incorporated (e.g., how to report AEs, all side effects listed
in IB, witness signatures on updated consents where required)

**Inconsistencies with Protocol**

It is expected that there is evidence that a check of the informed consent has been made
against the protocol

**Forms Not Updated with Amendments**

It is expected that there is evidence that QA check of the informed consent has been made
against any amendments to the protocol.

**Poor Version Control**

It has been observed on inspection that there is either no version control or the current
control has not been changed correctly resulting in same version numbers with different
dates etc.

**Incorrect Form Used**

At investigator sites there is a lack of control of the informed consent forms, thus
consistently see that old versions are used or wrong age range version in paediatric studies
etc.

**Unclear Process**

It is expected that there is a formal process for informed consent, especially with regard to
vulnerable subjects.

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**Best Intentions Can Lead to Inspection Findings**

There can be instances when you are trying to be helpful and aid the trial subject by filling
out some of the consent document for them. Although, this is done with the best of
intentions it can been seen as coercion as this finding from a site inspection shows:

> “The consent form should be personally signed and dated by the patients. In 3 out of 8
patients the consent form had the patient’s date and time completed by the investigator.”
According to Section 4.8 of ICH E6, neither the Investigator, nor the trial staff, should coerce or unduly influence a trial subject to participate or to continue to participate in a study.

Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

Therefore, in practice what this means is:

- The trial subject should personally sign and date the form followed by the Investigator (or delegate)
- The Investigator must not fill in any of the details for the trial subject (no matter how helpful) or complete the form before the trial subject
Clinical Trials: Study Conduct

Definitions

Audit:

- A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (As per Section 1.6 of ICH E6).

Case Report Form (CRF):

- A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject (As per Section 1.11 of ICH E6).

Essential Documents:

- Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see Section 8. Essential Documents for the Conduct of a Clinical Trial) (As per Section 1.23 of ICH E6).

- Refer to Section 8 of ICH E6 for the minimum list if essential documents which serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Inspection:

- The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority(ies) (As per Section 1.29 of ICH E6).
Monitoring:

- The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (As per Section 1.38 of ICH E6).

Source Data:

- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (As per Section 1.51 of ICH E6).

Source Documents:

- Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial) (As per Section 1.52 of ICH E6).

Protocol Compliance

Investigator Responsibilities

- ICH E6: Guideline for Good Clinical Practice
  - According to the guidance provided in Section 4.5 of ICH E6:
    - The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor
should sign the protocol, or an alternative contract, to confirm agreement (As per Section 4.5.1 of \textit{ICH E6}).

- The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)) (As per Section 4.5.2 of \textit{ICH E6}).

- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol (As per Section 4.5.3 of \textit{ICH E6}).

\textbf{Protocol Waivers}

- \textbf{MHRA GCP Website: GCP Frequently Asked Questions}
  - \textbf{Q:} Can Criteria Within the Protocol be Waivered?
  - \textbf{A:} The Clinical Trial Regulations (Regulation 29) state that no person shall conduct a trial other than in accordance with the protocol relating to that trial.
  - \textbf{A:} Adherence to the protocol is a fundamental part of the conduct of a clinical study. Any significant change to the protocol (in particular, changes to eligibility criteria) must be submitted as an amendment to the competent regulatory authority and Ethics Committee. Deviations from the inclusion / exclusion criteria of the protocol might erode the scientific and ethical value of the protocol and its authorisation and might have an impact on the processes put in place for the care and safety of the study subjects.

- \textbf{EMA Website: Questions and Answers on Protocol Waivers}
  - \textbf{Q:} Can a sponsor prospectively approve deviations (so-called “protocol waivers”) from the inclusion/exclusion criteria of the approved protocol without additional approval of the Ethics Committee and competent regulatory authority?
  - \textbf{A:} Adherence to the protocol is a fundamental part of the conduct of a clinical study. Any significant change to the protocol should be submitted as
an amendment to the competent regulatory authority and Ethics Committee. Significant changes to the protocol include any change in inclusion and exclusion criteria, addition or deletion of tests, dosing, duration of treatment etc (see the definition of a substantial amendment in the 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial' published by the European Commission in Chapter I, Volume 10 of The Rules Governing Medicinal Products in the European Community). Deviations from the inclusion / exclusion criteria of the protocol might erode the scientific and ethical value of the protocol and its authorisation and might have an impact on the processes put in place for the care and safety of the study subjects.

- **A**: Sponsors and investigators should not use systems of prospectively approving protocol deviations, in order to effectively widen the scope of a protocol. Protocol design should be appropriate to the populations required and if the protocol design is defective, the protocol should be amended.

- **A**: GCP does permit deviations from the protocol when necessary to eliminate immediate hazards to the subjects (Urgent Safety Measures – see below) but this should not normally arise in the context of inclusion/exclusion criteria, since the subject is not yet fully included in the trial at that point in the process GCP inspectors have observed a number of sponsors implementing systems where the investigator can contact the sponsor, usually the Medical Monitor, and request a prospective approval to deviate from the inclusion and/or exclusion criteria. The use of such systematic waiver systems in clinical trials is not considered to be appropriate and studies using such a system might be regarded as non-compliant with GCP.

**Urgent Safety Measures**

According to Regulation 30 of [SI 2004/1031](https://www法令通.com) as amended by [SI 2009/1164](https://www法令通.com), which states:

1. The sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.
2. If measures are taken pursuant to paragraph (1), the sponsor shall—
   - (a) where paragraph (3) applies, as soon as possible; and
(b) in any other case, immediately, and in any event no later than 3 days from the date the measures are taken,

give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

(3) This paragraph applies for any period during which a disease—

(a) is pandemic; and

(b) is a serious risk to human health or potentially a serious risk to human health.

### Serious Breach

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by SI 2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol. This transposed the reporting requirements of Section 5.20 of ICH E6 into UK law.

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by SI 2006/1928
  - Refer specifically to:
    - **Regulation 29A: Notification of Serious Breaches**

(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of—

(a) the conditions and principles of good clinical practice in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25,

within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree—

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.”.

- **MHRA GCP Website**: Guidance on the Notification of Serious Breaches of GCP:
This guidance:

- outlines the practical arrangements for notifications
- provides advice on what should and what should not be classified as a “serious breach” and what must be reported
- outlines possible actions that may be taken by the MHRA in response to notifications of serious breaches.

- **Notification of Serious Breaches of GCP or Trial Protocol form**

- **ICH E6**: Guideline for Good Clinical Practice

- **Refer specifically to:**

  - **Section 5.20: Non-Compliance**

  - Non-compliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor’s staff should lead to prompt action by the sponsor to secure compliance.

  - If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution’s participation in the trial. When an investigator's/institution’s participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

**Protocol Amendments**

Article 10(a) of the **2001/20/EC** allows amendments to be made to the conduct of a clinical trial after its commencement. It does not require notification of non-substantial amendments; only amendments that are substantial must be notified to the Competent Authority (CA) and Ethics Committee concerned (see Section 3 of **ENTR/CT1**). In addition when a sponsor and/or investigator must take urgent safety measures to protect the trial subjects from immediate hazard Article 10(b) of **2001/20/EC** allows them to do so before
notifying the CA, but they must notify them as soon as possible (As per Section 3.9 of ENTR/CT1).

**Protocol Amendments: Non-substantial Amendments**

The sponsor does not have to notify non-substantial amendments to the national competent authority or the Ethics Committee. However, non-substantial amendments should be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. This is of particular relevance for the Clinical Trial Application Form: This form should be updated in its entirety at the occasion of a substantial amendment. Documentation of non-substantial amendments should also be available on request for inspection at the trial site or the sponsor premises as appropriate (As per Section 3.6 of ENTR/CT1).

**Protocol Amendments: Substantial Amendments**

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial (As per Section 3.3 of ENTR/CT1).

Amendments to the trial are regarded as “substantial” where they are likely to have a significant impact on:

- The safety or physical or mental integrity of the subjects;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any IMP used in the trial.

In all cases, an amendment is only to be regarded as “substantial” when one or more of the above criteria are met.

The ‘Substantial Amendment Notification Form’ provides headings of aspects of a trial to which a sponsor might need to make a substantial amendment. The list is not exhaustive; a substantial amendment might occur in some other aspect of a trial. Not all amendments to those aspects of a trial need to be notified; only those that meet the criteria of “substantial” above.
Protocol Amendments: NRES Guidance

This site provides comprehensive guidance on what constitutes a substantial versus non-substantial amendment, how to notify and to whom.

- NRES Guidance: Notification of Amendments
  - Examples of substantial and non-substantial amendments
  - Requirements for favourable ethical opinion
  - Notices of substantial amendment
  - Submitting notices of substantial amendment
  - REC procedures for reviewing substantial amendments
  - Adding new sites and investigators
  - Urgent safety measures

NRES Guidance: Examples of Substantial Amendments

- The following amendments should normally be regarded as substantial:
  - Changes to the design or methodology of the study, or to background information affecting its scientific value;
  - Changes to the procedures undertaken by participants; any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;
  - Significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers;
  - A change of sponsor(s) or sponsor’s legal representative;
  - Appointment of a new chief investigator or key collaborator;
  - A change to the insurance or indemnity arrangements for the study;
  - Inclusion of a new trial site (not listed in the original application) in a CTIMP;
  - Appointment of a new principal investigator at a trial site in a CTIMP;
Temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;

A change to the definition of the end of the study; any other significant change to the protocol or the terms of the REC application.

Some changes, however, will have no significant implications for participants or for the conduct, management or scientific value of the study and can be regarded as ‘non-substantial’ or ‘minor’ amendments.

You must inform the main REC of all substantial amendments by completing a notice of substantial amendment. Non-substantial amendments do not need to be notified.

**NRES Guidance: Examples of Non-Substantial Amendments**

- Examples of non-substantial amendments might be as follows:
  
  - Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
  
  - Updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);
  
  - Changes to the chief investigator’s research team (other than appointment of key collaborators);
  
  - Changes to the research team at particular trial sites (other than appointment of a new principal investigator in a CTIMP);
  
  - Changes in funding arrangements;
  
  - Changes in the documentation used by the research team for recording study data;
  
  - Changes in the logistical arrangements for storing or transporting samples;
  
  - Inclusion of new sites and investigators in studies other than CTIMPs;
  
  - Extension of the study beyond the period specified in the application form.

Changes to contact details for the sponsor (or the sponsor’s representative), chief investigator or other study staff are minor amendments but should be notified to the main REC for information. You should notify both the main REC and the relevant local REC if the principal investigator's contact details have changed.
The Case Report Form (CRF) and Data Entry

Specific guidance on the Investigator’s responsibility with respect to the completion of CRFs and amendment to data entries is provided in Section 4.9 of ICH E6.

CRF Data Entry

- The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports (As per Section 4.9.1 of ICH E6).

- Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained (As per Section 4.9.2 of ICH E6).

Changes or Correction to a CRF

- Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see Section 5.18.4(n) of ICH E6). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor’s designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections (As per Section 4.9.3 of ICH E6).

Monitoring

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (As per Section 1.38 of ICH E6).

The purposes of trial monitoring are to verify that:

a) The rights and well-being of human subjects are protected.

b) The reported trial data are accurate, complete, and verifiable from source documents.
c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

(Source: Section 5.18.1 of ICH E6)

- **ICH E6**: Guideline for Good Clinical Practice
  - Refer to Section 5.18 for comprehensive guidance on:
    - The purpose of Monitoring
    - The Selection and Qualification of Monitors
    - Extent and Nature of Monitoring
    - Monitor’s Responsibilities
    - Monitoring Procedures
    - The Monitors Report
**Clinical Trials: Safety Reporting**

The reader is directed towards the [MHRA Pharmacovigilance Learning Module](https://www.mhra.gov.uk/guidance/pharmacovigilance-learning-module), which will help you to learn what pharmacovigilance is and how it relates to day-to-day clinical practice. You will understand health professionals’ role in contributing to clinical knowledge on the harms of individual medicines and you will learn how to keep updated on the risks of medicines—so you make good treatment choices.

**Definitions**

**Definition: Adverse Event**

- Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (As per Annex 1 of ETR/CT3, Article 2(m) of 2001/20/EC and Section II.A.1 of ICH E2A).

- *Comment:* An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product (As per Annex 1 of ETR/CT3).

**Definition: Adverse Reaction of an Investigational Medicinal Product**

- All untoward and unintended responses to an investigational medicinal product related to any dose administered (As per Annex 1 of ETR/CT3, Article 2(n) of 2001/20/EC and Section II.A.2 of ICH E2A).

- *Comment:* All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship (As per Annex 1 of ETR/CT3).

**Definition: Pharmacovigilance**

- Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse
effects of medicines, biological products, herbals and traditional medicines with a view to:

- Identifying information about potential new hazards
- Preventing harm to patients.

- The word is derived from the Greek pharmakon - drug, and the Latin vigilare - to be awake or alert, to keep watch (MHRA Website – Good Pharmacovigilance Practice)

**Definition: Severity**

- The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria (As per Annex 1 of ENTR/CT3).

**Definition: Serious Adverse Event or Serious Adverse Reaction**

- Any untoward medical occurrence or effect that at any dose:
  - results in death,
  - is life-threatening
  - requires hospitalisation or prolongation of existing inpatients’ hospitalisation,
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly or birth defect.

(As per Annex 1 of ENTR/CT3, Article 2(o) of 2001/20/EC and Section II.B of ICH E2A).

- **Comments**: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe (As per Annex 1 of ENTR/CT3).

- Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious (As per Annex 1 of ENTR/CT3).
Definition: Unexpected Adverse Reaction

- An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product) (As per Annex 1 of ENTR/CT3, Article 2(p) of 2001/20/EC and Section II.A.3 of ICH E2A).
- *Comments:* When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected (As per Annex 1 of ENTR/CT3).

Summary of the Safety Reporting Timeframes

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Reporting Timeframe(s)</th>
<th>Reference(s)</th>
</tr>
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<tbody>
<tr>
<td>Urgent Safety Measures</td>
<td>• 3 days from the point the measure was taken&lt;br&gt;• Or “as soon as possible” in the case of a pandemic</td>
<td>• Section 4.5.4 of ICH E6&lt;br&gt;• Article 10(b) of 2001/20/EC&lt;br&gt;• Regulation 30 of SI 2004/1031 as amended by SI 2009/1164</td>
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<td></td>
<td>➔ Report to concerned Competent Authorities and Ethics Committees</td>
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<tr>
<td>SUSAR (Fatal or Life-threatening)</td>
<td>• 7 days after knowledge by the Sponsor of such a case.&lt;br&gt;• A further 8 days is allowed for the provision of relevant follow-up information</td>
<td>• Section III.B.1 of ICH E2A&lt;br&gt;• Article 17.1(a) of 2001/20/EC&lt;br&gt;• Regulation 33 of SI 2004/1031</td>
</tr>
<tr>
<td></td>
<td>➔ Report to concerned Competent Authorities and Ethics Committees</td>
<td></td>
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<tr>
<td>SUSAR (All Other)</td>
<td>• As soon as possible, but within a maximum of 15 days of first knowledge by the Sponsor</td>
<td>• Section III.B.2 of ICH E2A&lt;br&gt;• Article 17.1(b) of 2001/20/EC&lt;br&gt;• Regulation 33 of SI 2004/1031</td>
</tr>
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<td></td>
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Pharmacovigilance Resources

- Refer to the MHRA Pharmacovigilance Learning Module
Safety Reporting in Clinical Trials: Global Guidance

- **ICH E2A**: Clinical Safety Data Management - Definitions and Standards for Expedited Reporting
  - Refer specifically to:
    - **Section II**: Definitions and Terminology Associated With Clinical Safety Experience
    - **Section III**: Standards for Expedited Reporting
      - What Should be Reporting
      - Reporting Timeframes
      - Minimum Criteria for Reporting
      - How to Report
      - Managing Blinded Therapy Cases
      - Informed Investigators and Ethics Committees of New Safety Information
    - **Attachment 1**: Key Data Elements for Inclusion in Expedited Reports of Serious Adverse Drug Reactions
- **ICH E2B**: Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports E2B(R2)
  - **ICH E2B Questions and Answers (R5), March 2005**
- **Council for International Organizations of Medical Sciences (CIOMS)**
  - Refer to the short six page report entitled “WHAT IS CIOMS?” published in 2009 for further information
  - **CIOMS I. (1990) International Reporting of Adverse Drug Reactions**
    - The most valuable outcome of the working group of CIOMS I was the introduction of the "CIOMS I Reporting Form" for standardized international reporting of individual cases of serious, unexpected adverse drug reactions.
Safety Reporting in Clinical Trials: European Commission Directive(s)

- The Clinical Trials Directive (2001/20/EC)
  - Refer specifically to:
    - Article 16: Notification of Adverse Events
    - Article 17: Notification of Serious Adverse Reactions

Safety Reporting in Clinical Trials: European Commission Guidance

- ENTR/CT3: Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
- ENTR/CT4: Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance - Clinical Trial Module)

Safety Reporting in Clinical Trials: EudraVigilance

- EudraVigilance
  - EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).
  - EudraVigilance supports in particular the:
    - Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the European Medicines Agency (EMA), national Competent Authorities, marketing authorisation holders, and sponsors of clinical trials in the EEA;
    - Early detection of possible safety signals associated with medicinal products for Human Use;
Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions;

Decision making process, based on a broader knowledge of the adverse reaction profile of medicinal products especially in the frame of Risk Management.

Taking into account the pharmacovigilance activities in the pre- and post-authorisation phase, EudraVigilance provides two reporting modules:

- The EudraVigilance Clinical Trial Module (EVCTM) to facilitate the electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) as required by Directive 2001/20/EC.

Safety Reporting in Post-Marketing Studies: European Guidance

- Eudralex Volume 9A: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (September 2008)
  - Relates primarily to the post-marketing safety reporting requirements for medicinal products for Human use.

Safety Reporting in Clinical Trials: UK Law and Practical Guides

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)
  - Refer specifically to:
    - Part 5: Pharmacovigilance
      - Regulation 32: Notification of Adverse Events
      - Regulation 33: Notification of Suspected Unexpected Serious Adverse Reactions (SUSARs)
      - Regulation 34: Clinical Trials Conducted in Third Countries
• **Regulation 35**: Annual List of Suspected Serious Adverse Reactions and Safety Report

• **The MHRA Good Pharmacovigilance Practice Guide (Nov 2008)**
  
  
  o This guide is primarily geared towards the post-marketing aspects of safety reporting but there is still a good deal of relevant and helpful information about safety reporting in clinical trials.

  ▪ Refer Specifically to:

  • **Section 12.3**: Safety Reporting for Intervventional Clinical Trials
    
    o **Section 12.3.1**: Causality Assessments
    
    o **Section 12.3.2**: Investigator’s Brochure
    
    o **Section 12.3.3**: What is a SUSAR?
    
    o **Section 12.3.4**: Reporting Requirements for IMPs
    
    o **Section 12.3.5**: Reporting Requirements for Non-IMPs
    
    o **Section 12.3.6**: Electronic Reporting
    
    o **Section 12.3.7**: Considerations for Blinded Trials
    
    o **Section 12.3.8**: Annual Safety Reports
    
    o **Section 12.3.9**: Safety Monitoring Boards
    
    o **Section 12.3.10**: Safety Reporting to Ethics Committees

  • **Table A3.2**: UK Clinical Trial Legislation Relating to Safety Reporting

  • **Annex 4**: Safety Reporting Requirements for Clinical Studies

    o Provides a tabulated overview of the safety reporting requirements for:
      
      ▪ Intervenional Clinical Trials
      
      ▪ Non-Investigational Medicinal Products
Non-Interventional Studies

- Commercial pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to identifying new information about hazards associated with medicines and preventing harm to patients. Pharmacovigilance is particularly concerned with adverse drug reactions. This text complements current legislation and guidance and provides practical advice about achieving an appropriate system of pharmacovigilance.

UK Regulatory Authority (MHRA)

- MHRA Website: Clinical Trial Authorisations: Safety Reporting - SUSARS and ASRs

  - This section provides information on safety reporting for clinical trials for medicines. The requirements for safety reporting can be found in Part 5 (Regulations 32, 33, 34 and 35) of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)

MHRA Pharmacovigilance Learning Module

- MHRA Pharmacovigilance Learning Module

  - Here, you will learn what pharmacovigilance is and how it relates to day-to-day clinical practice. You will understand health professionals’ role in contributing to clinical knowledge on the harms of individual medicines and you will learn how to keep updated on the risks of medicines—so you make good treatment choices.

  - Key points
    - Information on potential harm of a medicine is incomplete when the medicine is launched
    - Pharmacovigilance is vital to ensure the continued safety of medicines
    - Health professionals, pharmaceutical companies and regulators play a key role in pharmacovigilance
The Yellow Card Scheme is an important method by which potential adverse drug reactions can be detected.

To safeguard individuals’ health, clinicians need to seek out emerging information on adverse reactions to medicines and to act on it.

Information on adverse drug reactions is covered in the BNF and the medicine’s summary of product characteristics; important emerging information is provided by bulletins such as Drug Safety Update.

**Investigator Responsibilities**

- The investigator shall report any serious adverse event (SAE), which occurs in a subject immediately to the Sponsor.

- The immediate report may be made orally or in writing and shall be followed by a detailed written report on the event.

- Where the event reported consists of, or results in, the death of a subject, the investigator shall supply the Sponsor with any additional information requested by the Sponsor. Where the death has been reported to the relevant Ethics Committee, the investigator shall supply any additional information requested by that Committee.

**How to Report Suspected Unexpected Serious Adverse Reactions (SUSARs)**

- **eSUSAR**
  - From 1\(^{st}\) January 2010 all sponsors should submit all UK relevant SUSARs electronically ([eSUSAR](#)). However, there will be a 3 month period during which the [CIOMS 1 form](#) will still be accepted for reporting SUSARs.
  - When completing the CIOMS form, Sponsors should include the EudraCT number, CTA number (or DDX/CTX number), protocol number and study name.

**MHRA Website: Good Pharmacovigilance Practice**

- [MHRA Website: Good Pharmacovigilance Practice](#)
Safety Reporting in Clinical Trials: Reports Required by UK Ethics Committees

Safety Reports for CTIMPS

- NRES Guidance: [Safety Reports for CTIMPs](#)

Safety Reports for all Other Research

- NRES Guidance: [Safety Reports for all Other Research](#)
Urgent Safety Measures

According to Regulation 30 of SI 2004/1031 as amended by SI 2009/1164, which states:

(1) The sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

(2) If measures are taken pursuant to paragraph (1), the sponsor shall—

(a) where paragraph (3) applies, as soon as possible; and

(b) in any other case, immediately, and in any event no later than 3 days from the date the measures are taken,

give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

(3) This paragraph applies for any period during which a disease—

(a) is pandemic; and

(b) is a serious risk to human health or potentially a serious risk to human health.

MedDRA

- MedDRA Definition and MSSO Website

  - MedDRA - the Medical Dictionary for Regulatory Activities - is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines). Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products. MedDRA was developed by the International Conference on Harmonisation (ICH) and is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH steering committee.

  - The MSSO - Maintenance and Support Services Organization - serves as the repository, maintainer, and distributor of MedDRA as well as the source for the most up-to-date information regarding MedDRA and its application within the biopharmaceutical industry and regulators. MedDRA subscribers submit proposed changes to the terminology. The MSSO includes a group of
internationally based physicians who review all proposed subscriber changes and provide a timely response directly to the requesting subscriber.

- **MedDRA Background Information**: Via the EudraVigilance Website
Clinical Trials: Study Completion

Definitions

Definition: End of Trial Notification

- The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be notified as a substantial amendment. In most cases it will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this should be justified in the protocol (As per Section 2.5 of ENTR/CT1).

End of Trial Notification

Clinical Trials: End of Trial Notification Timeframe

- According to Article 10(c) of 2001/20/EC:

  - Within 90 days of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned and the Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

- According to Regulation 27 of SI 2004/1031:

  1. Subject to paragraph (2), within 90 days of the conclusion of a clinical trial the sponsor shall notify the licensing authority and the relevant ethics committee in writing that the trial has ended.
  2. If a trial is terminated—

     a. before the date for the conclusion of the trial specified in the protocol for that trial, or
     b. before the event specified in the protocol as the event which indicates the end of the trial has occurred,
the sponsor shall notify the licensing authority and the relevant ethics committee in writing of the termination of the trial within 15 days of the date of termination.

(3) A notification made in accordance with paragraphs (1) or (2) shall contain the particulars specified in Part 4 of Schedule 3.

Clinical Trials: When is the End of the Trial?

- According to Section 2.5 of ENTR/CT1:
  
  o The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be notified as a substantial amendment. In most cases it will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this should be justified in the protocol.

Clinical Study Report

Clinical Study Report: Reporting Timeframe

- According to Section 4.3 of ENTR/CT1:
  
  o The clinical trial summary report is part of the end of trial notification, albeit usually submitted only subsequently to the end of trial notification. The sponsor should provide this summary report within one year of the end of the complete trial for non-paediatric clinical trials. For paediatric clinical trials, the timelines are set out in the Commission Communication 2009/C28/01. Regarding the arrangements for submitting the clinical trial summary report, its format, content, and its accessibility for the public, reference is made to the Commission Communications 2009/C28/01 and 2008/C168/02 and their implementing technical guidance documents

Clinical Study Report: Structure and Content

- ICH E3: Structure and Content of Clinical Study Reports
The objective of this guideline is to allow the compilation of a single core clinical study report acceptable to all regulatory authorities of the ICH regions. The regulatory authority specific additions will consist of modules to be considered as appendices, available upon request according to regional regulatory requirements.

The guideline is intended to assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy to review. The report should provide a clear explanation of how the critical design features of the study were chosen and enough information on the plan, methods and conduct of the study so that there is no ambiguity in how the study was carried out. The report with its appendices should also provide enough individual patient data, including the demographic and baseline data, and details of analytical methods, to allow replication of the critical analyses when authorities wish to do so. It is also particularly important that all analyses, tables, and figures carry, in text or as part of the table, clear identification of the set of patients from which they were generated.
Clinical Trials: Quality Control, Audits and Inspection

Definitions

Quality Assurance (QA):

- All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (as per Section 1.46 of ICH E6).

Quality Control (QC):

- The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (as per Section 1.47 of ICH E6).

Audit:

- A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (as per Section 1.6 of ICH E6).

Inspection:

- The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority(ies) (as per Section 1.29 of ICH E6).

European GCP Inspection Standards and Guidelines

Eudralex Volume 10: Chapter IV - Inspections
Refer to Chapter IV (Inspections) of Eudralex Volume 10, which covers the following areas:

- Guidance for the preparation of GCP inspections (June 2008)
- Recommendation on inspection procedures for the verification of good clinical practice compliance (July 2006)
- Guidance for the conduct of GCP inspections (June 2008)
- Annex I to Guidance for the conduct of GCP inspections – investigator site (June 2008)
- Annex II to Guidance for the conduct of GCP inspection – clinical laboratories (June 2008)
- Annex III to Guidance for the conduct of GCP inspections – computer systems (June 2008)
- Annex IV to Guidance for the conduct of GCP inspections – Sponsor and CRO (June 2008)
- Annex V to Guidance for the conduct of GCP inspections – Phase I Units (November 2008)
- Annex VI to Guidance for the conduct of GCP inspections - Record keeping and archiving of documents (March 2010)
- Guidance for coordination of GCP inspections and co-operation between GCP inspectors, the reference and concerned Member States and CMD(h), in the context of the evaluation of the GCP compliance of marketing authorization applications for mutual recognition and decentralized procedures (June 2009)
- Guidance for exchange of GCP Inspection Reports according to Article 15(2) of Directive 2001/20/EC (revision 1 – May 2009)
- Guidance for the communication on GCP inspections and findings (June 2008)
- Procedure for standardisation of GCP inspection entries in EudraCT (November 2008)
Guidance for the preparation of Good Clinical Practice inspection reports (June 2008)

Recommendations on the qualifications of inspectors verifying compliance in clinical trials with the provisions of Good Clinical Practice (July 2006)

European Medicines Agency: GCP Inspections

- European Medicines Agency (EMA): GCP Inspections
  - GCP Inspectors Working Group
  - Inspection Procedures and Guidance for GCP Inspections Conducted in the Context of the Centralised Procedure
  - GCP Questions and Answers
    - Questions and Answers on Investigational Medicinal Products (IMPs) in Bioavailability and Bioequivalence Trials
    - Questions and Answers on GCP Matters
    - Questions and Answers on Records of Study Subject Data Relating to Clinical Trials

UK GCP Inspection Standards and Guidelines

MHRA Inspection Websites

- MHRA Website: Pharmaceutical Industry - Inspection
  - This section provides links to information about the different types of inspection, including the inspection process and risk-based inspections, as well as the associated legislation and guidance.
    - Good Clinical Practice (GCP)
      - GCP: Risk Based Inspections
      - GCP: The Inspection Process
      - GCP: Frequently Asked Questions
• **GCP for Clinical Laboratories**
  - Good Pharmacovigilance Practice (GPvP)
    - **GPvP: The Inspection Process**
    - **GPvP: Risk Based Inspections**
    - **Frequently Asked Questions for GPvP**
  - **Risk Based Inspections**
  - Good Manufacturing Practice (**GMP**)
  - Good Laboratory Practice (**GLP**)
  - Good Distribution Practice (**GDP**)

**Guidance on Inspection Preparation**

- **NHS R&D Forum**
  - How to prepare for an inspection for Good Clinical Practice by the Medicines and Healthcare products Regulatory Agency (MHRA): a guide for NHS organisations that sponsor or host clinical trials of medicinal products (Version 3, November 2007)

**UK GCP Audit Standards and Guidelines**

**British Association of Research Quality Assurance (BARQA)**

The British Association of Research Quality Assurance (**BARQA**) is an association dedicated to informing and advancing its members, BARQA provides status and visibility for individuals concerned with the quality of research in pharmaceutical, agrochemical and chemical industry sectors. Since its inception in 1977 the Association has grown and developed to reflect regulatory changes, the impact of regulatory inspection and the changing structure and needs of industry.