GCP Considerations: Informed Consent

Guidance on Informed Consent in Clinical Trials: UK

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Table of Contents

Index of Tables

Index of Figures

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Introduction

This document aims to provide some clarity and guidance on the current regulatory framework, which governs informed consent in clinical trials within the UK. It should be noted that the 'Common Law' element of the regulatory framework has not been discussed in this document

A Word of Caution: The regulations and guidelines, which apply to the field of clinical research, are rapidly evolving and adapting. As such, the reader must understand that this document is supplied only as a 'guidance' or 'considerations' tool.

The reader should always check the validity and current nature of the information provided with local authorities and/or research ethics committees before starting clinical research activities and ensure that they comply with the applicable regulations and guidelines.

Informed Consent

Informed Consent Definitions

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).

The Declaration of Helsinki (1996 Version)

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).

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)).

Recent History

The past 80 years has seen many great medical achievements and advancements. Unfortunately, along the way there have also been many human tragedies and atrocities such as the Nazi and Japanese human 'medical' experiments of the second world war, the Tuskegee syphilis study and Thalidomide, to name but a few.

What follows below is a very brief overview of the human tragedies that led to the formation of the ethical principles, guidelines and regulations that we now know as Good Clinical Practice (GCP) and which govern clinical research and clinical trials.

Nazi War 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. These experiments included:

- Experiments on twins
- Freezing experiments
- Malaria experiments
- Mustard gas experiments
- Sulfonamide experiments
- Sea water experiments
- Sterilization experiments
- Experiments with poison
- Incendiary bomb experiments
- High altitude experiments

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.

The Japanese also conducted similar human experiments during the Second World War, although these are less well known for various reasons, most of which are political. Those who wish to know more should seek out information on 'Unit 731'.

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 (refer to Figure 1).

Figure 1 – The Nuremburg Code

1. 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.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

"Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.]

Source: http://www.hhs.gov/ohrp/archive/nurcode.html

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.

According to the 2008 Version of the Declaration of Helsinki:

Section A.6: In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

Section B.11: It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

Section B.24 (Informed Consent): In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

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. Everyone involved in clinical research should be encouraged to read this short document.

- Declaration of Helsinki (1989 Version) – Last version acknowledged by the USA legislation (e.g., 21 CFR 312.120 which no longer refers to the Declaration of Helsinki bur rather refers to 'GCP'))
- Declaration of Helsinki (1996 Version) – Version referenced throughout European legislation
- Declaration of Helsinki (2000 Version)
- Declaration of Helsinki (2008 Version)

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 - Eva Mozes-Kor

Recommended Reading:

- The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation. Edited by George J Annas and Michael A Grodin. Oxford University Press. ISBN 0-19-510106-5

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.

> "Men who were poor and African American, without resources and with few alternatives believed they had found hope when they were offered free medical care by the United States Public Health Service. They were betrayed.
>
> For 40 years, hundreds of men were betrayed, along with their wives and children, along with a community in Macon County, Alabama, the City of Tuskegee, the fine university there, and the larger African American community. The United States government did something that was wrong – deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all of our citizens."
>
> President Bill Clinton, 16th May 1997

* The Tuskegee Syphilis Study - Author: Fred D Gray; ISBN: 1-58838-089-0

Source: http://www.cdc.gov/tuskegee/clintonp.htm

The Tuskegee syphilis study reaffirmed the principle that prior informed consent should be obtained from individuals before they are allowed to participate in human experimentation.

Part C.1 of the Belmont Report deals specifically with informed consent and states that:

> "Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied"

Further information can be found at:

- U.S. Public Health Service Syphilis Study at Tuskegee
- Tuskegee University - Research Ethics: The Tuskegee Syphilis Study

Recommended Reading:

- The Tuskegee Syphilis Study: An Insiders Account of the Shocking Medical Experiment Conducted by Goverment Doctors Against Africa American Men. Author, Fred D Gray. NewSouth Books. ISBN 1-58838-089-0
    - Fred D Gray was the attorney for the men of the Tuskegee study

The Thalidomide Tragedy

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 1 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).

German pediatricians and geneticists began to see children with gross limb malformations of a most unusual pattern. When two cases were shown at a pediatric meeting in Kassel by Kosenowand Pfeiffer in October 1960, few people present had ever seen similar limb defects. Wiedemann in 1961 described 13 affected infants who had been referred to him over a period of 10 months, and noted that this amounted to an epidemic. He drew attention to a number of associated malformations in these children, including congenital heart disease, microphthalmos and coloborna, intestinal atresis, renal malformations, abnormal pinnae, and facial nacvus (Smithells & Newman, 1992).

In November 1961, Lenz suggested that these deformities resulted from the mothers having taken thalidomide. By a remarkable coincidence, the same suggestion was made at much the same time by McBride in Australia. Confirmation of this suggestion came rapidly from all parts of the British Isles, Kenya, Japan, Sweden, Belgium, Switzerland, Lebanon, Israel, Peru, Canada, Brazil, the Netherlands, and the USA. The drug had been released only for clinical trials in the USA because of concerns following reports from Europe of irreversible peripheral neuritis as a side effect of thalidomide. Consequently there were very few cases. By contrast, it had been on sale over the counter in Germany, and there were consequently more affected children there than anywhere else. In the UK the drug was available on prescription only, but it was used very widely for, among other problems, common symptoms of early pregnancy (Smithells & Newman, 1992).

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).

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:

- Smithells RW and Newman CGH. Recognition of thalidomide defects. J Med Genet 1992; 29: 716-723 (Link to Full Article)
- 'The History of Thalidomide' by Professor Dr. W. Lenz
- THE THALIDOMIDE TRAGEDY - Extract from the German jubilee publication "Unser Weg 1946-2006: 60 Jahre Grünenthal GmbH"

From Human Abuse to Regulated Use

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 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.

Since 1965 there has been a plethora of clinical trial-related guidelines and regulations which has culminated in the adoption of the ICH Guideline for Good Clinical Practice (ICH E6)

in 1996 and the publication of the Clinical Trials Directive (2001/20/EC) in 2001 and the GCP Directive (2005/28/EC) in 2005 with their subsequent adoption and enforcement into UK law in 2004 (SI 2004/1031) and 2006 (SI 2006/1928), respectively (refer to Figure 2 and Figure 3)

Figure 2 – 'Cause & Effect' Timeline of the Human Tragedies that have led to the Clinical Research Guidelines and Regulations of Today

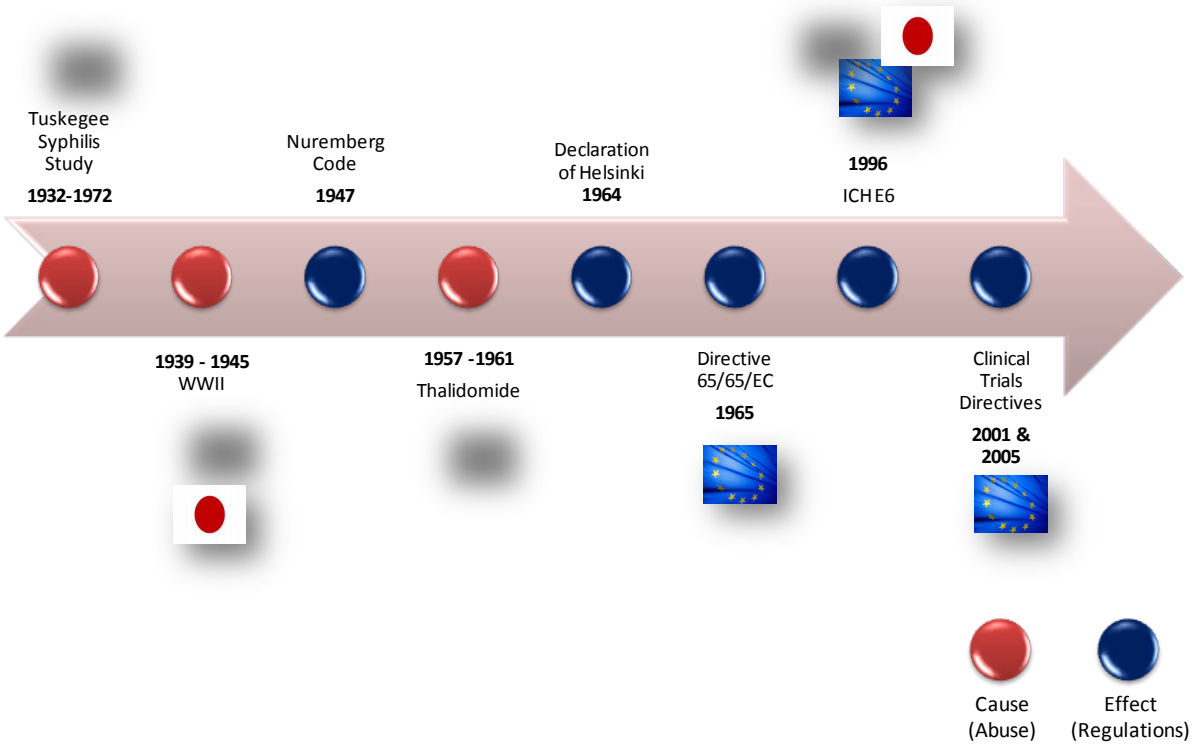
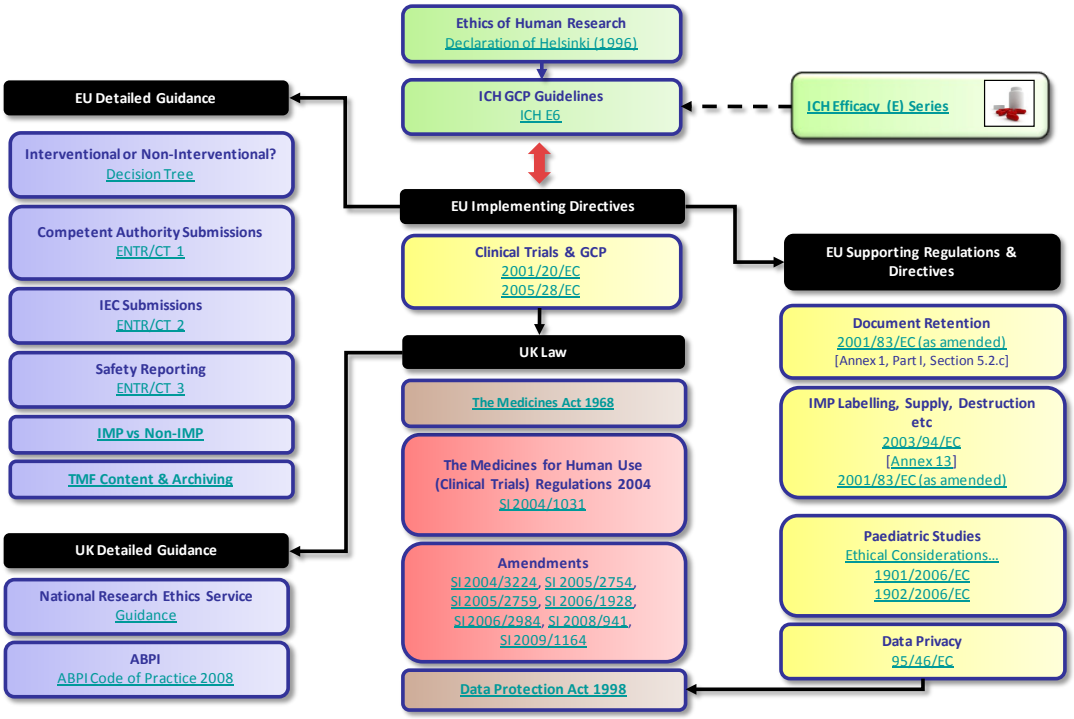


Figure 3 – Overview of the Clinical Trials Regulatory Framework in Europe

Note: A hyperlinked version of this figure is available to down load from the CHCUK Website

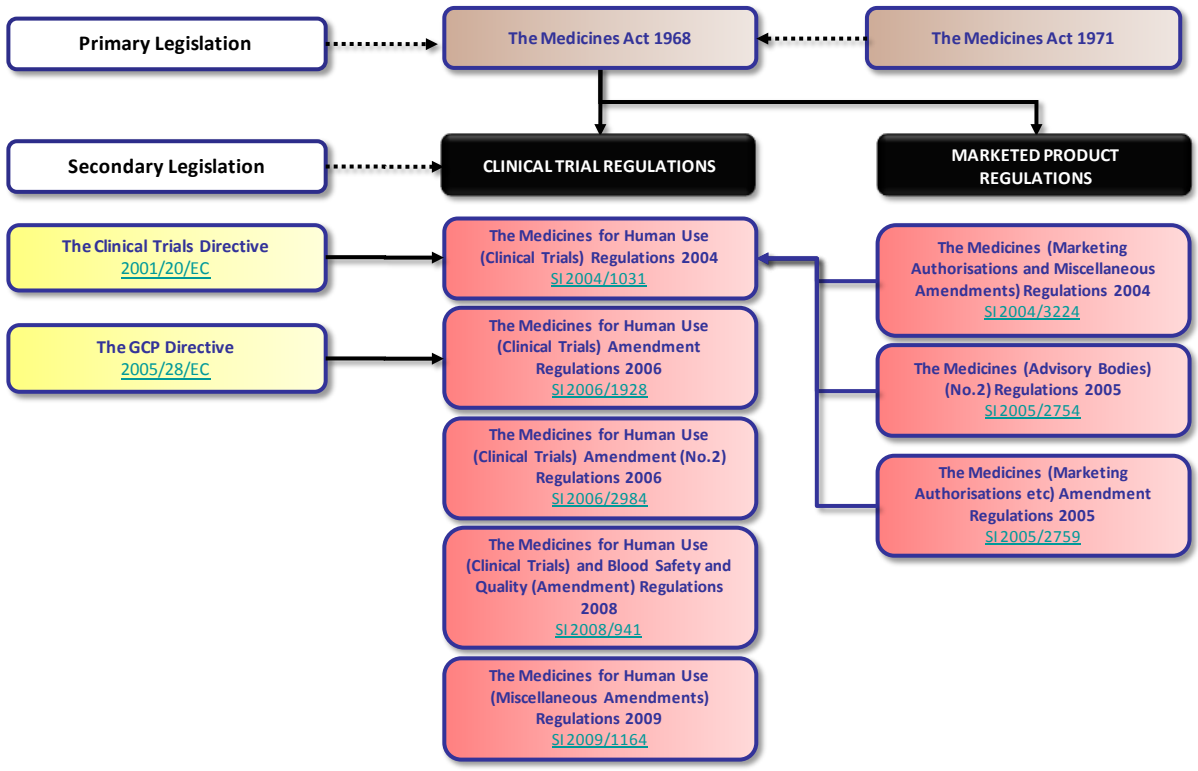


Informed Consent - Regulatory Framework

There is sometimes confusion regarding which regulations and guidelines we should follow be following 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 implements 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 (refer to Figure 4).

Figure 4 – Overview of the Clinical Trials Regulatory Framework in the UK

Note: A more comprehensive overview and summary of the UK clinical trial regulations is available on the CHCUK website.



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.

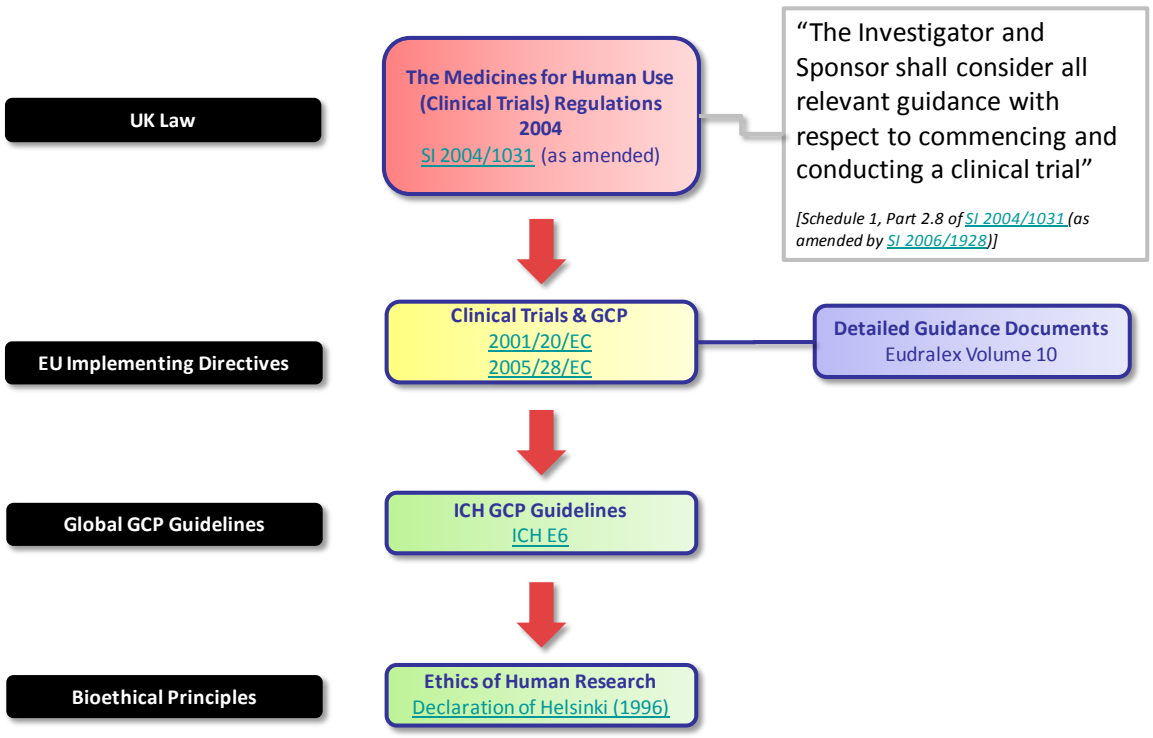
The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) do not contain all of the information necessary for running a clinical trial as this would make them unmanageable.

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 when managing and conducting clinical trials. This is illustrated below in Figure 5 and is particularly relevant when discussing informed consent (as per Section 4.8 of ICH E6).

Figure 5 – Overview of the Regulatory Foundations for Clinical Trials in the UK and the Relevance of the European Directives , ICH Guidelines and Bioethical Principles of the Declaration of Helsinki



Informed Consent - Regulatory Framework in Europe and the UK

The following table (refer to Table 1) provides a very high level overview of the informed consent regulatory framework (Legislation and Guidelines) present in Europe and implemented in the UK.

Table 1 - Overview of the Informed Consent Regulatory Framework in Europe and the UK

Regulation/ Guideline	Reference	Applicability	Detail
ICH E6	Section 4.8	'Global'	Sets out the principles and details of informed consent
ICH E11	Section 2.6.3	'Global'	Provides guidance on the principles and details of informed consent/ assent for trials in minors/ paediatrics
2001/20/EC	Article 2(j)	EU	Defines Informed Consent
2001/20/EC	Articles 3 - 5	EU	Set out the principles of informed consent
Ethical Considerations		EU	Provides detailed guidance on the consent/ assent considerations for trials in minors
SI 2004/1031 (as amended)*	Schedule 1, Parts 1 – 5	UK	Set out the conditions and principles in relation to informed consent
SI 2006/2984		UK	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 • Implements Section 4.8.15 of ICH E6
SI 2008/941		UK	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

Regulation/ Guideline	Reference	Applicability	Detail
			• Implements Section 4.8.15 of ICH E6
NRES Guidance on PILs & ICFs		UK	Provides guidance and templates for PILs and ICFs
NRES Information Paper on Informed Consent in Clinical Trials (2008)		UK	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

The basic 'building blocks' and 'additional considerations' for the patient information leaflet and informed consent form can be found in Section 4.8 of ICH E6 (refer to Table 2 and Table 3).

Table 2 - The Basic Building Blocks of Informed Consent

ICH E6 Section	Basic Building Blocks
4.8.6	Wording
4.8.10 (a) (f)	Research Notion
4.8.10 (b) (h)	Goals of the Trial
4.8.10 (c)	Design of the Trial
4.8.10 (h)	Expected Therapeutic Benefits
4.8.10 (i)	Alternative Treatments
4.8.10 (m)	Voluntary Nature of the Participation
4.8.10 (m)	Withdraw from the Trial without Prejudice
4.8.10 (q)	Contact Point
4.8.10 (p)	Informed of New Data that May Influence Decision to Participate
4.8.10 (r)	Stopping the Trial
4.8.10 (e)	Subject's Responsibilities
4.8.10 (s)	Length of Study
4.8.10 (t)	Recruitment

ICH E6 Section	Basic Building Blocks
4.8.10 (d)	Invasive Procedures
4.8.10 (g)	Foreseeable Risks
4.8.10 (j)	Compensation and/or treatment available in the event of a trial-related injury
4.8.10 (j)	Third Party Liability
4.8.10 (l)	Payment and Costs
4.8.10 (k)	Remuneration
4.8.10 (o)	Data Confidentiality
4.8.10 (n)	Access to Records

Table 3 - Informed Consent: Additional Considerations

ICH E6 Section	Additional Considerations
4.8.15	Emergency Situations
4.8.12 to 4.8.15	Enrolment of 'legally incompetent' subjects – Minors – Incapacitated Adults

Informed Consent – General Considerations

The following should be considered when obtaining informed consent from trial subjects (as per Section 4.8 of ICH E6):

- Before informed consent may be obtained, the Investigator should provide the subject with ample time and opportunity to inquire about details of the trial.
- The Investigator should fully inform the subject of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the EC and MHRA.
    - Must ensure that only the current approved version of the informed consent information/documentation is used
- The subject should receive a copy of the signed and dated informed consent form and any other written information provided to subjects.
    - This includes any subsequent amendments to the form and/or information

Informed Consent: UK

Regulatory Overview

Competent Authority:	Medicines and Healthcare products Regulatory Agency (MHRA)
Research Ethics Committees (RECs):	National Research Ethics Service (NRES) (The National Research Ethics Service (NRES) is the administrative body responsible for providing advice, assistance and operational support to NHS RECs for the whole of the UK)
Data Protection Agency:	The Information Commissioner's Office (ICO)

Regulatory Bodies

Competent Authority (MHRA)

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).

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.

Research Ethics Committees (NRES)

Ethics committees with the competence to review clinical trial investigational medicinal products (CTIMPs) must be recognised by the United Kingdom Ethics Committee Authority (UKECA), which is a body established under the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031 as amended).

There are currently 3 types of recognised committee in the UK:

- **Type 1:** Recognised to review phase 1 trials in healthy volunteers for the whole of the UK.
- **Type 2:** Recognised to review trials in patients being conducted within a single geographical domain of the UK.

- **Type 3:** Recognised to review trials in patients for the whole of the UK.

In addition, there is one specialised ethics committee, the Gene Therapy Advisory Committee (GTAC), which is responsible for review of trials of gene therapy (EFGCP Report, UK).

As of January 2009 there were 141 ethics committees in the UK (England 112, Scotland 17, Wales 9, Northern Ireland 3). Not all RECs are recognised to review CTIMPs and some RECs can be both Type 1 (for Phase 1 studies) and Type 3. Of these there are:

- 7 Type 1 recognised committees (including 7 non-NHS committees)
- 6 Type 2 recognised committees in Scotland only
- 57 Type 3 recognised committees

and the Gene Therapy Advisory Committee, *and* the MoD REC (EFGCP Report, UK).

Other RECs are authorised to review non-CTIMP trials.

Process for Obtaining Ethical Review by a Research Ethics Committee in the UK

The Chief Investigator must apply for ethics committee opinion to a recognised ethics committee, depending on the type of trial. Application to any recognised ethics committee within the NHS must be made via the Integrated Research Application System (IRAS). IRAS will capture all information a researcher needs to submit for the relevant permissions and approvals to enable the conduct of health and social care research (EFGCP Report, UK).

Data Protection (ICO)

The Information Commissioner's Office (ICO) is the UK's independent authority set up to uphold information rights in the public interest, promoting openness by public bodies and data privacy for individuals.

Notification

Notification is a statutory requirement and every organisation that processes personal information must notify the Information Commissioner's Office (ICO), unless they are exempt. Failure to notify is a criminal offence.

Notification is the process by which a data controller gives the ICO details about their processing of personal information. The ICO publishes certain details in the register of data controllers , which is available to the public for inspection.

Refer to:

- ICO Guidelines on Notification Under the Data Protection Act 1998
- ICO Notification handbook: A Complete Guide to Notification
- ICO Guidance on the Data Protection Act
- Data Protection Act 1998 (as amended)

Country-Specific Informed Consent Considerations

Considerations	Details
Single REC Opinion:	**YES**
Consent Age:	**16** The following guidance applies to England, Wales, Scotland and Northern Ireland without distinction. *Definition of a minor* Under the Regulations a minor is a person under the age of **16** years (as per Regulation 2 of SI 2004/1031 as amended) (Refer also to paragraphs 13 and 14 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008)
Core ICH E6 Elements:	**YES** (Refer to Tables F1 and F2)
Conditions which Apply in Relation to an Adult able to Consent or Who has Given Consent Prior to the Onset of Incapacity:	Under Part 3 of Schedule 1 to the Principal Regulations (SI 2004/1031) (implementing Article 3(2) to 2001/20/EC) the following conditions apply to the giving of informed consent by a capable adult: 1. The subject has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. 2. The subject has been informed of his right to withdraw from the trial at any time. 3. The subject has given his informed consent to taking part in the trial. 4. The subject may, without being subject to any resulting

Considerations	Details
	detriment, withdraw from the clinical trial at any time by revoking his informed consent. 5. The subject has been provided with a contact point where he may obtain further information about the trial. If a capable adult gives informed consent to take part in a clinical trial of an IMP (CTIMP) in accordance with these conditions, and subsequently becomes unable to give informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. If a capable adult refuses informed consent, and subsequently becomes unable to give informed consent, the refusal is legally binding. He or she cannot be entered into the trial by seeking consent from a legal representative. (as per Part 3 of Schedule 1 of SI 2004/1031 as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164) (Refer also to paragraphs 10, 11 and 12 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008)
Conditions and Principles which Apply to the Inclusion of an Incapacitated Adult in a Clinical Trial:	The following conditions and principles are listed in Part 5 of Schedule 1 to the Principal Regulations (SI 2004/1031) and implement Article 5 of 2001/20/EC. **Conditions** 1. The legal representative has had an interview with the investigator, or another member of the investigating team, in which opportunity has been given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. 2. The legal representative has been provided with a contact point where further information about the trial may be obtained. 3. The legal representative has been informed of the right to withdraw the subject from the trial at any time. 4. The legal representative has given informed consent to the subject taking part in the trial. 5. The legal representative may, without the subject being subject to any resulting detriment, withdraw the subject from the trial at any time by revoking the informed consent. 6. The subject has received information, according to his or her capacity of understanding, about the trial and its risks and benefits. 7. The investigator must consider the explicit wish of a subject capable of forming an opinion and assessing the information

Considerations	Details
	provided. This applies both to the wish of a subject to refuse to take part, or to withdraw from the trial at any time. 8. No incentives or financial inducements are given either to the subject or to the legal representative, except the provision of compensation for injury or loss. 9. There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit. 10. The trial is essential to validate data obtained (a) in other clinical trials involving persons able to give informed consent, or (b) by other research methods. 11. The clinical trial relates directly to a life-threatening or debilitating clinical condition from which the subject suffers. **Principles** 12. Informed consent given by a legal representative shall represent the presumed will of an incapacitated adult. 13. The trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the cognitive abilities of the patient. 14. The risk threshold and the degree of distress have to be specially defined and constantly monitored. 15. The interests of the patient always prevail over those of science and society. (as per Part 5 of Schedule 1 of SI 2004/1031 as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164)
Conditions and Principles which Apply to the Inclusion of a Minor in a Clinical Trial:	The following conditions and principles are listed in Part 4 of Schedule 1 to the Principal Regulations (SI 2004/1031) and implement Article 4 of 2001/20/EC. **Conditions** 1. The parent or legal representative has had an interview with the investigator, or another member of the investigating team, in which opportunity has been given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. 2. The parent or legal representative has been provided with a contact point where further information about the trial may be obtained. 3. The parent or legal representative has been informed of the right to withdraw the minor from the trial at any time. 4. The parent or legal representative has given informed consent to the minor taking part in the trial. 5. The parent or legal representative may, without the minor

Considerations	Details
	being subject to any resulting detriment, withdraw the minor from the trial at any time by revoking the informed consent. 6. The minor has received information, according to his or her capacity of understanding, about the trial and its risks and benefits. The information must be given by staff with experience with minors. 7. The investigator must consider the explicit wish of a minor capable of forming an opinion and assessing the information provided. This applies both to the wish of a minor to refuse to take part, or to withdraw from the trial at any time. 8. No incentives or financial inducements are given either to the minor or to the parent or legal representative, except the provision of compensation for injury or loss. 9. The clinical trial relates directly to a condition from which the minor suffers or is of such a nature that it can only be carried out on minors. 10. Some direct benefit for the group of patients involved in the trial is to be obtained from the trial. 11. The trial is necessary to validate data obtained (a) in other clinical trials involving persons able to give informed consent, or (b) by other research methods. 12. The corresponding scientific guidelines of the European Medicines Agency (EMEA) are followed. **Principles** 13. Informed consent by a parent or legal representative shall represent the minor's presumed will. 14. The trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the minor's stage of development. 15. The risk threshold and the degree of distress have to be specially defined and constantly monitored. 16. The interests of the patient always prevail over those of science and society. (as per Part 4 of Schedule 1 of SI 2004/1031 as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164)
Emergency Situations (Incapacitated Adult):	The Medicines for Human Use (Clinical Trials) (Amendment No.2) Regulations 2006 (SI 2006/2984) made additional provision relating to trials involving incapacitated adults in emergency situations. Where the treatment to be given to an incapacitated adult as part of the trial needs to be given urgently, time may not allow for the written consent of a legal representative to be obtained first. The amendment allows incapacitated adults to be entered into a trial prior to consent being obtained from a legal representative provided that:

Considerations	Details
	• Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency but • It is not reasonably practicable to obtain informed consent prior to entering the subject, and • The action to be taken is carried out in accordance with a procedure approved by the ethics committee. Where an incapacitated adult is recruited in an emergency situation without prior informed consent, steps must be taken to seek informed consent either from the subject (if capacity has been recovered) or from a legal representative as soon as practicable after the initial emergency has passed. Where consent is withheld, the subject must be withdrawn from the trial. (Refer to paragraphs 21 and 22 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008)
Emergency Situations (Minors):	The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality Amendment) Regulations 2008 (SI 2006/2984) made additional provision relating to trials involving minors in emergency situations. Where the treatment to be given to a minor as part of the trial needs to be administered urgently, time may not allow for the written consent of a person with parental responsibility or a legal representative to be obtained first. The amendment allows minors to be entered into a trial prior to informed consent being obtained provided that: • Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency but • It is not reasonably practicable to obtain informed consent prior to entering the subject, and • The action to be taken is carried out in accordance with a procedure approved by the ethics committee. Where a minor is recruited in an emergency situation without prior informed consent, steps must be taken to seek informed consent from a person with parental responsibility or a legal representative as soon as practicable after the initial emergency has passed. Where consent is withheld, the subject must be withdrawn from the trial. (Refer to paragraphs 16 and 17 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008)
Hierarchy of Consent (Incapacitated Adults):	Table 4 (see below) sets out the hierarchy prescribed in the Regulations (SI 2004/1031 as amended) for determining what type of legal representative should be approached to give

Considerations	Details
	informed consent on behalf of an incapacitated adult prior to inclusion of the subject in the trial. The provisions in England, Wales and Northern Ireland differ from those in Scotland. (Refer to paragraph 20 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008)
Hierarchy of Consent (Minors):	The Regulations (SI 2004/1031 as amended) prescribe a hierarchy for determining who should be approached to give informed consent on behalf of a minor prior to their inclusion in the trial (Refer to Table 5 below). The provisions for informed consent by a legal representative only apply if by reason of the emergency nature of the treatment provided as part of the trial no person with parental responsibility can be contacted prior to the proposed inclusion of the minor. (Refer to paragraph 15 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008)

Informed Consent – Detailed Considerations

Table 4 - Hierarchy of Informed Consent for an Incapacitated Adult

Source: Table 2 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008

England, Wales, and Northern Ireland	Scotland
1. Personal legal representative A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the adult, *and* (b) available and willing to do so.	*1. Personal legal representative* 1A. Any guardian or welfare attorney who has power to consent to the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.
2. Professional legal representative A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board).	*2. Professional legal representative* A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider.

England, Wales, and Northern Ireland	Scotland
A professional legal representative may be approached if no suitable personal legal representative is available.	A professional legal representative may be approached if it is not reasonably practicable to contact either 1A or 1B before the decision to enter the adult into the trial is made. Informed consent must be given before the subject is entered into the trial.

Table 5 - Hierarchy of Informed Consent for a Minor

Source: Table 1 of the NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008

	Person who may give consent	Definition	Commentary
1	Parent	A parent or person with parental responsibility.	Should always be approached if available.
2	Personal legal representative	A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the minor, and (b) available and willing to do so.	May be approached if no person with parental responsibility can be contacted prior to the proposed inclusion of the minor, by reason of the emergency nature of the treatment provided as part of the trial.
3	Professional legal representative	A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the medical treatment of the minor, or (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board).	May be approached if no person suitable to act as a personal legal representative is available. Informed consent must be given before the minor is entered into the trial

Informed Consent Guidance and Templates

- NRES (PIL and ICF Guide): NRES guidance on information sheets and consent forms v3.5 May 09
    - All researchers involved in the development of patient information sheets and informed consent forms for UK clinical trials should read this document

- Provides detailed guidance on:
  - The principles and process of informed consent
  - Patient information sheets
  - Informed consent forms

- NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008
  - 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

- SI 2004/1031 - The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164)
  - Refer specifically to Regulation 2.1 and Schedule 1
  - Refer to the CHCUK GCP Regulatory Maps for an up to date summary of the amendments to SI 2004/1031

Applicable Legislation

The laws and guidelines which are applicable to the management and conduct of informed consent include (but are not limited to):

- SI 2004/1031 - The Medicines for Human Use (Clinical Trials) Regulations 2004
  - As amended by:
    - SI 2006/1928 - The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
    - SI 2006/2984 – The Medicines for Human Use (Clinical Trials) Amendment (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

  - Refer to the CHCUK GCP Regulatory Maps for a current summary of the amendments to SI 2004/1031

- The Data Protection Act 1998 (Original)
  - Data Protection Act 1998 (as amended)
- NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008
- NRES (PIL and ICF Guide): NRES guidance on information sheets and consent forms v3.5 May 09

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

Presented in October 2006 at the MHRA Conference: Evolution of GCP inspection – From Process to Compliance.

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 (eg 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.

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

Useful Links

Data Protection

- The Information Commissioner's Office
- ICO Guidelines on Notification Under the Data Protection Act 1998
- ICO Notification handbook: A Complete Guide to Notification
- ICO Guidance on the Data Protection Act
- Department of Health: Guidance to the NHS on the Data Protection Act 1998

Department of Health

- Department of Health's Research Governance Framework: Research Governance Framework for Health and Social Care (2nd Edition, 2005)

UK Ethical Review Process

- National Research Ethics Service (NRES)
- NRES (Guidance)
- NRES SOP (April 2009) - Standard Operating Procedures for Research Ethics Committees
- NRES (PIL and ICF Guide): NRES guidance on information sheets and consent forms v3.5 May 09
- NRES information paper on informed consent in clinical trials of investigational medicinal products v3 May 2008
- Integrated Research Application System (IRAS)
- EFGCP Report, UK: The EFGCP Report on the Procedure for the Ethical Review of Protocols for Clinical Research Projects in the UK (Update: April 2010)

UK Competent Authority & Clinical Trial Regulations

- Medicines and Healthcare products Regulatory Agency (MHRA)
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)

- Refer to the CHCUK GCP Regulatory Maps for a current summary of the amendments to SI 2004/1031
- The UK Clinical Research Regulations: Consolidated and Indexed - Canary Ltd

Research Using Human Tissue

- Human Tissue Act 2004
- Human Tissue (Scotland) Act 2006
  - Refer to the CHCUK Human Tissue Research Regulatory Maps for a current overview of the regulation of human tissue research in the UK
- Human Tissue Authority (HTA)
- HTA Code of Practice 9 (Research) – Human Tissue Authority's (HTA) Code of Practice on Research using Human Tissue

Research using Mentally Incapacitated Subjects

- The Adults with Incapacity (Scotland) Act 2000
  - Applicable to trial subjects in Scotland
- The Mental Capacity Act 2005
  - Applicable to trial subjects in England & Wales

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