Non-Interventional Studies: Europe (Part 2)
Considerations when Managing and Conducting Non-Interventional Studies in Europe: Austria, Bulgaria, Cyprus, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Malta, Norway, Romania, Slovakia, Slovenia and the United Kingdom

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DISCLAIMER

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Introduction

This document aims to provide some clarity and guidance on the current regulatory frameworks, which govern non-safety, related Non-Interventional Studies (NIS) within Europe. This is therefore an ideal ‘considerations’ tool for managers and medical directors who are directly and indirectly involved in the conduct and/or management of NIS within multiple European countries.

Non-interventional studies (NIS) play a very important role in the development and life-cycle management of medicinal products. However, unlike clinical trials, which are comprehensively governed throughout Europe by the Clinical Trials Directive (2001/20/EC) and the GCP Directive (2005/28/EC), NIS (especially those studies which are not post-authorisation safety studies) have for many years lain in a regulatory grey zone.

Chapter I.7 of Eudralex Volume 9a does provide guidance for the management and conduct of post-authorisation safety-type NIS, but leaves the reader unclear as to what, if anything, applies to NIS, which are not safety-related.

The report therefore aims to provide some clarity with respect to the regulatory framework within which non-safety related NIS currently sit.

A Word of Caution: This is a rapidly changing field and as such the user is encouraged to seek confirmation of the approval and notification requirements prior to embarking upon an NIS.
Non-Interventional Studies

Definitions

Post-authorization Study

Any study conducted within the conditions laid down in the summary of product characteristics and other conditions laid down for the marketing of the product under normal conditions of use. A post-authorization study falls either within the definitions of a clinical trial or a non-interventional study and may also fall within the definition of a post-authorization safety study (Annex 1.1 of Eudralex Volume 9A).

Post-authorization Safety Study (PASS)

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product (Article 1.15 of Directive 2001/83/EC).

Non-Interventional Study

A study where the medicinal product is 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 (Article 2(c) of 2001/20/EC).

It is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice (Section 1, Chapter I.7 of Eudralex Volume 9A).
NIS Regulations and Guidelines

Europe – General Considerations

It is recognised that at the time of authorisation, there is only a limited amount of information available on both the safety and efficacy of a medicinal product. Non-interventional post-authorisation studies are therefore aimed to complement the information obtained during clinical development of the medicinal products prior to authorisation.

NIS studies should not be planned and conducted for the purpose of promoting medicines, but rather should be conducted for a scientific purpose i.e., to gather ‘real-life’ information on the drugs practices etc (Section 5, Chapter I.7, Eudralex Volume 9a).

For a study to be ethically justifiable it must be well designed and meet the basic ethical principles contained in the Declaration of Helsinki of the World Medical Association on ethical principles for medical research on humans, and its subsequent revisions.

In Europe, NIS are regulated through the provisions of Article 97 and Title IX of 2001/83/EC (as amended) which has led to the empowerment of self-regulation bodies such as EFPIA and the publication of specific guidance on the conduct and management of NIS in Eudralex Volume 9a. Admittedly, the context of this published guidance is primarily post-authorisation safety studies, but the general rules do apply.

The general recommendations in Chapter I.7 of Eudralex Volume 9a include:

- Adherence to the highest possible standards of professional conduct and confidentiality.
- Provision of a protocol.
- Compliance with data protection legislation.
- Ethical review of the protocol.
- Notification of intent to the Competent Authority.
- Exclusion of Marketing Representatives i.e., involvement in the recruitment of physicians and patients could be seen as promotional activity.
- Fair remuneration.
- Provision of progress reports and a final report to the Competent Authority.
Publication of results.

In spite of the publication of these guidelines in 2007, there has been a large degree of confusion with regard to their applicability to non-safety related NIS which has led to the publication of specific and detailed guidelines by the Pharmaceutical Industry Self-Regulation Bodies in Europe; specifically the European Federation of Pharmaceutical Industries and Associations (EFPIA) in October 2007 and the subsequent adoption of the EFPIA guidance into the applicable country-specific codes of practice (e.g., ABPI in the UK).

The guidance provided in Section 15 of the EFPIA “Code on the Promotion of Prescription-Only Medicines to, and Interaction with, Healthcare Professionals” complements that published in Chapter I.7 of Eudralex Volume 9a.

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 (NIS or Clinical Trial?)

The recent inclusion of specific guidance on the conduct of NIS in the European Federation of Pharmaceutical Industries and Associations (EFPIA) 2007 Code of Practice, as amended in 2011 (EFPIA COP), and the subsequent adoption of this guidance into the codes of practice of the EFPIA member organisations - has been a huge step forward in harmonising the standards applied to these types of studies. However, the regulatory governance of NIS still suffers from significant disharmony across Europe, with some countries implementing very specific and detailed legislation (e.g., Spain and Austria) and others having no legislation at all.

As a consequence, those individuals responsible for the conduct and management of NIS within Europe are faced with the daunting challenge of understanding, and complying with, a diverse range of country-specific regulations and guidelines.

This report aims to help alleviate this ‘pain’ by providing a summary of the relevant country-specific regulations and guidelines in a single document.

Figure 1 illustrates how the various regulations and guidelines tie together.

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* The ‘NIS or Clinical Trial?’ algorithm can also be found at the end of – The European Commission’s (Eudralex Volume 10) Guidance Documents Applying to Clinical Trials: ‘Questions and Answers’, Version 9, August 2011
Ethical Considerations


Medicinal Products in the EU and, for clinical trials, the Guidelines for Good Clinical Practice (Commission Directive 2005/28/EC) should also be followed (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

Consideration of ethical issues, data ownership and privacy is an important part of the International Society for Pharmacoepidemiology (ISPE) guideline for Good Pharmacoepidemiology Practices (GPP), section IV. It includes a sub-section (IV.A) on protection of human subjects and a reference to the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health. The GPP also recommends a stand-alone section within the protocol containing a description of plans for protecting human subjects that includes consideration of the need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee and the requirement of informed consent in accordance with local law (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

The main scope of the International Epidemiological Association (IEA) Good Epidemiological Practice (GEP) guideline for proper conduct in epidemiological research is on the ethical principles of pharmacoepidemiological field studies, which could also apply to interventional studies, such as the role of ethics committees, patients’ informed consent, use and storage of personal data and publication of results (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

The Council for International Organizations of Medical Sciences (CIOMS) 2009 International Ethical Guidelines for Epidemiological Studies have as their objective the preparation of guidelines to indicate how the ethical principles that should govern the conduct of biomedical research involving human subjects could be effectively applied. The Guidelines set forth ethical guidance on how epidemiologists - as well as those who sponsor, review, or participate in the studies they conduct - should identify and respond to the ethical issues that are raised by the process of producing this information (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

The Agency for Healthcare Research and Quality (AHRQ) of the United States has published Registries to Evaluate Patient Outcomes: a User’s guide, Second Edition, which is a reference for establishing, maintaining and evaluating the success of registries created to collect data about patient outcomes. In Section 1: ‘Creating a registry’ is a specific chapter dedicated to ethics, data ownership, and privacy. The concepts are useful although the authors indicate that this section focuses solely on United States (US) law (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

The Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (ICJME) includes clear statements on
ethical principles related to publication in biomedical journals addressing authorship and contributorship, editorship, peer review, conflicts of interest, privacy and confidentiality and protection of human subjects and animals in research (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

From the examples provided above, it may be seen that there is a wide range of documents for protection of human subjects. The applicability of ethical requirements, however, varies based on the nature of the inquiry and the studies to be conducted. Certain human subject protections applicable to clinical studies (e.g. full informed consent) would not apply to other kinds of research (e.g. review of data from de-identified medical records). Furthermore, while protection of privacy is paramount, there may be situations in which the use of data for secondary analyses has public health benefits (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

Data Privacy

In Europe, European Union (EU) and national laws are the keys to what may and may not be done with regard to data access, data linkage and consent issues, including such domains as human rights and duty of confidentiality. While differing data custodians currently have differing requirements related to what approvals are needed before data can be released, the requirements will fit within the overall need to meet all applicable EU and national laws and guidelines for the actual study. This includes situations where multi-country studies are being conducted and there may be transfer of data or information. In addition to meeting legislative requirements, studies also need to adhere to a set of principles that meet with the requirements of scientific and ethical reviews (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

EFPIA Code of Practice

The guidance provided in Section 15 of the 2011 EFPIA Code of Practice complements that published in Chapter I.7 of EudraLex Volume 9A. The EFPIA Code of Practice begins by capturing all prospective NIS within the scope of the requirements, thus removing any confusion that may have previously resulted from the guidance provided in EudraLex Volume 9A. In particular, Section 15 of the EFPIA Code of Practice requires that

- The study is conducted for a scientific purpose
- There is a written study plan (protocol)
There are written contracts between the study sponsor and healthcare professionals and/or institutions.

Any remuneration provided is reasonable and reflects fair market value.

The study protocol should be submitted for review in those countries where ethics committees are prepared to review the document.

Local data privacy laws, rules and guidelines must be respected.

The study protocol must be approved by, and the study conduct supervised by, the company’s scientific service.

The study results must be analysed and made available within a reasonable period of time to the company’s scientific service and the healthcare professionals who participated in the study.

If the study shows results that are important for the assessment of the benefit/risk profile of the medicinal product, the summary report should be immediately forwarded to the relevant competent authority.

Medical sales representatives may only be involved in an administrative capacity and such involvement must be under the supervision of the company’s scientific service.

Companies are encouraged publicly disclose the summary details and results of non-interventional studies in a manner consistent with the parallel obligations for clinical trials.

Companies apply the same requirements (to the extent applicable) to all other types of studies, including epidemiological studies, registries and other studies that are retrospective in nature.

The adoption of guidance specific to NIS across Europe is certainly a step in the right direction. However, those individuals and organisations responsible for the management and conduct of NIS across Europe find themselves in a similar situation to those involved in clinical trials before the implementation of the Clinical Trials Directive (2001/20/EC). That is, there is an acknowledged need for these studies and a rudimentary regulatory framework in place, but it is disjointed, driven by individual countries and lacking harmonisation. Although we have certainly taken a step in the right direction, there remains a long and bumpy journey ahead.
Country-Specific Considerations for Conducting and Managing NIS

The rest of this report focuses on summarising the country-specific regulations and guidelines applicable to the conduct and management of non-interventional studies within Europe and is intended as a knowledge management tool.

The report directs the user to the applicable:

- Competent Authority
- Ethics Committee(s)
- Data Protection Agency
- Pharmaceutical Self-Regulatory Body
- Regulations and guidelines

Useful Links

CHCUK Resources (Relating to Non-Interventional Studies)

NIS Definitions

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 Considerations Newsletter

- We provide a free bi-monthly newsletter which is available to everyone and which aims to supplement the information provided in the NIS Reports
- All of the back issues of the NIS Considerations newsletter are now available to browse through the link provided.

NIS Training

CHCUK provide bespoke training solutions for NIS. The link provided is an example of a generic UK-based introduction to the requirements for non-interventional studies.
CHCUK Resources (Relating to Non-Interventional Studies)

Non-interventional Studies:
- What are they?
- How do they differ from clinical trials?

NIS Reports

CHCUK produces detailed reports, which capture the country-specific regulations and guidelines applicable to non-interventional studies (NIS). These NIS reports have been developed as an aid for anyone responsible for managing and/or conducting non-interventional studies throughout Europe.

NIS REPORT PART 1 - 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 - 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

Bespoke NIS Reports

As well as the resources and information provided on the website we also prepare bespoke reports for clients. To date we have covered the NIS requirements in the following regions:
- Europe
- Latin America
- Russia
- South Africa

NIS Useful Links

http://www.chcuk.co.uk/nisresources.html

European Pharmaceutical Industry Self-regulatory Body

European Federation of Pharmaceutical Industries and Associations (EFPIA)

http://www.efpia.org/Content/Default.asp

EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare

http://extranet.efpia.eu/docs/1/DHFJGEAADOFPBKGOHEOFAH5H4D41YHAV6474I5143/EFPIA/docs/D
**European Pharmaceutical Industry Self-regulatory Body**

Professionals (June 2011)

Accessed From:


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**European Commission Regulations, Directives and Guidelines**

**The Clinical Trials Directive (2001/20/EC)**


Accessed From:


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

Accessed From:


**The Data Privacy Directive (95/26/EC)**

Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of such Data

Accessed From:


**Directive 2001/83/EC (as amended)**


Accessed From:


**Regulation (EC) No 45/2001**

Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data

Accessed From:


**Regulation (EC) No 726/2004**

Regulation (EC) No 726/2004 Of The European Parliament And Of The Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines
European Commission Regulations, Directives and Guidelines

Agency

Eudralex Volume 9a


Refer to:

- Question 1.9: What can be considered a “non-interventional trial”?
- Annex: Decision tree to establish whether a trial is a “clinical trial”

NIS Ethical Principles and Guidelines

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (2008)

ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (1996)


Pharmacoepidemiologic studies provide valuable information about the health effects of healthcare products. The ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) are intended to assist investigators with issues pertaining to the planning, conduct, and evaluation of pharmacoepidemiologic research. The first revision, in 2004 revised and superseded the Guidelines for Good Epidemiologic Practice (GEP) developed in 1996. In that revision, the scope of the guidelines was broadened geographically and conceptually, to reflect ISPE’s international membership, to include risk management and pharmacoeconomic activities, and to address more clearly the role of epidemiologic studies from industry and regulatory perspectives. Specifically, the 2004 revision provided
NIS Ethical Principles and Guidelines

guidance on regulatory reporting requirements as they relate both to individual cases and to aggregate data (see, VI. Adverse Event Reporting). The focus of the second revision has been on the use and communication of statistical measures and to add clarification to specific items throughout the document.

IPSE Guidance: Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health (1998)  
http://www.pharmacoepi.org/resources/privacy.cfm

The GRACE Principles (2010)  

CIOMS International Ethical Guidelines for Epidemiological Studies (2009)  
http://www.cioms.ch/

STROBE Statement  
http://www.strobe-statement.org/


The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP): Guide on Methodological Standards in Pharmacoepidemiology (August 2011)  

ENCePP Checklist for Study Protocol (August 2011)  

ENCePP Standards and Guidelines  
http://www.encepp.eu/standards_and_guidances/index.html

ENCePP Code of Conduct  

ENCePP Register of Studies  
http://www.encepp.eu/encepp_studies/index.html#studyregister
Summary of the Country-Specific Considerations for Conducting Non-Interventional Studies
Country-Specific Considerations for Conducting Non-Interventional Studies
# UK

## Regulatory Overview

<table>
<thead>
<tr>
<th>Competent Authority:</th>
<th>Medicines and Healthcare products Regulatory Agency (MHRA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Ethics Committees:</td>
<td>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)</td>
</tr>
<tr>
<td>Data Protection Agency:</td>
<td>The Information Commissioner’s Office (ICO)</td>
</tr>
<tr>
<td>Pharmaceutical Self-Regulation Body:</td>
<td>The Association of the British Pharmaceutical Industry (ABPI)</td>
</tr>
<tr>
<td>Pharmaceutical Code of Practice</td>
<td>ABPI Code of Practice (2011) (Referred to as the ABPI COP in the following text)</td>
</tr>
</tbody>
</table>

## Summary of the Legal & Regulatory Provisions

<table>
<thead>
<tr>
<th>Competent Authority (MHRA)</th>
<th>Prospective NIS*</th>
<th>Retrospective NIS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Approval</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Research Ethics Committee (NRES)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable Opinion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Submit annual progress reports</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Submit applications for substantial amendments</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Provide end of trial notifications</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Submit a final study report</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Report SAEs</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NHS R&amp;D Trust</td>
<td>Approval</td>
<td>✓</td>
</tr>
<tr>
<td>Data Protection Agency (ICO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notification</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmaceutical Self-Regulation Body (ABPI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Company’s Scientific Service shall approve and supervise NIS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Written contracts must be in place which provide a detailed description of the services expected from the investigators as well as of the amount and the procedures for remunerating the investigators which must reflect fair market value</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>The Company should comply with legislation on personal data protection which includes obtaining informed consent (where appropriate)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Study results to be analysed and reports thereof must be submitted within a reasonable period of time to the Company’s Scientific Service</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Company should send the executive summary of the study results to all healthcare professionals that participated in the study</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If the study results are important for the assessment of benefit-risk, the summary report should be immediately forwarded to the relevant competent authority</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Companies must publish the summary details and results of non-interventional studies of marketed medicines in a manner consistent with their parallel obligations with respect to clinical trials.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>The QPPV must provide, as soon as is reasonably practicable, to the licensing authority any other information relevant to the evaluation of the benefits and risks afforded by a</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
medicinal product, including appropriate information arising from the use of the product in post-authorisation safety studies

<table>
<thead>
<tr>
<th></th>
<th>Prospective NIS*</th>
<th>Retrospective NIS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>The study must not constitute an inducement to recommend, prescribe, purchase or sell, supply or administer medicinal products</td>
<td>✔</td>
<td>✓</td>
</tr>
</tbody>
</table>

*The guidance provided by the ABPI COP is aimed at prospective studies with the proviso that similar principles are applied to the conduct of retrospective studies. NRES doesn’t delineate between Prospective and retrospective studies per se.

^ An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was: Related – that is, it resulted from administration of any of the research procedures, and Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence (as per NRES Guidance on Safety Reporting for Non-CTIMPs).

Red highlighted text denotes country-specific considerations.
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 (RECs)

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) (EFGCP Report, UK 2011).

There are currently 2 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 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 and clinical trials of stem cell therapy involving ‘cells derived from stem cell lines’ (EFGCP Report, UK 2011).

Ethical Review of Research Studies other than Clinical Trials

Research studies other than CTIMPs are reviewed by NHS Research Ethics Committees (RECs), which are established under policy from the relevant Health Departments in each of the four UK countries (EFGCP Report, UK 2011).

The relevant departmental bodies are:

- Department of Health (England)
Under arrangements agreed between the four UK Health Departments, 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, including those recognised by UKECA. NRES provides support to RECs through a regional network of operational managers. It also administers a system of accreditation based on self-assessment and audit (EFGCP Report, UK 2011).

NRES also supports the Social Care REC (SCREC), which was established in 2009 to review non-clinical research with users of social care services. The SCREC is appointed by and is accountable to the Social Care Institute of Excellence, but has adopted the NRES SOPs and uses the Integrated Research Application System (IRAS) (EFGCP Report, UK 2011).

Other research, such as NIS (classed as ‘Non-CTIMPs’ by NRES) (whether single or multi-site) which is being undertaken anywhere in the UK is booked via Local Allocation Systems (EFGCP Report, UK 2011).

NHS RECs have generic expertise and may review all types of research. The NRES operating system provides for a single ethical review of any research project, in line with the system for CTIMPs under the EU Directive. Generally speaking, a NHS REC may give an ethical opinion that applies to the whole of the UK (EFGCP Report, UK 2011).

The one exception to this is research, other than CTIMPs, involving participants who are unable to consent for themselves and taking place both in Scotland and in England/Wales. In this case, separate reviews are required under the different legislation applying to such research in Scotland and in England/Wales respectively. The Adults with Incapacity (Scotland) Act 2000 requires such research to be reviewed by “the Ethics Committee” constituted under the Act. This Committee is currently Scotland Research Ethics Committee A. In England and Wales, the Mental Capacity Act 2005 requires approval of the research by a NHS REC established in England or Wales (EFGCP Report, UK 2011).

Data Protection Agency (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**

The Data Protection Act 1998 requires every data controller who is processing personal information in an automated form to notify, unless they are exempt. Failure to notify is a criminal offence. Register entries have to be renewed annually. If you are required to notify but don’t renew your registration, you are committing a criminal offence.

**What are the Exemptions from Notification?**

Most organisations that process personal data must notify the ICO. However, there are some exemptions.

By working through question 1-9 of the [online self-assessment](#) or by downloading the [Notification exemptions – self-assessment guide](#) you will be able to determine whether you need to notify.

Data controllers who are exempt from notification must comply with the other provisions of the Act, and may choose to notify voluntarily.

**Pharmaceutical Self-Regulation Body (ABPI)**

The Association of the British Pharmaceutical Industry (ABPI) is the trade association for more than 90 companies in the UK producing prescription medicines for human use. Its member companies research, develop, manufacture and supply more than 80 per cent of the medicines prescribed through the National Health Service (NHS).

The [ABPI](#) is the UK self-regulation Pharmaceutical body affiliated with [EFPIA](#).

**Applicable Legislation**

Non-interventional studies (NIS) are controlled by a combination of legislation and codes of practice in the UK.

The Medicines for Human Use (Clinical Trials) Regulations 2004 ([SI 2004/1031](#)) provide the legal definition for a non-interventional trial/study. However, according to the guidance provided by the MHRA ([MHRA Website - Clinical trial authorisations: Is a clinical trial authorisation required?](#)), and Regulation 2 of [SI 2004/1031](#), the UK clinical trial regulations do not apply to non-interventional studies.
This reflects Article 1.1 of the Clinical Trials Directive (2001/20/EC), which is implemented into UK law by SI 2004/1031 and states that “this Directive does not apply to non-interventional trials”.

The laws and guidelines that are applicable to the management and conduct of non-interventional studies in the UK include (but are not limited to):

<table>
<thead>
<tr>
<th>UK Laws and Guidelines</th>
<th>Accessed From:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Refer to the CHCUK GCP Regulatory Maps for an up to date summary of the amendments to SI 2004/1031</td>
<td></td>
</tr>
<tr>
<td>NRES Guidance on IRAS</td>
<td><a href="http://www.nres.npsa.nhs.uk/applications/integrated-research-application-system/">http://www.nres.npsa.nhs.uk/applications/integrated-research-application-system/</a></td>
</tr>
<tr>
<td>NRES Guidance: After ethical review - guidance for sponsors and investigators (research other than CTIMPs) (v4.0, September 2011)</td>
<td><a href="http://www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=11397">http://www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=11397</a></td>
</tr>
<tr>
<td>NRES Guidance on Annual Progress Report Requirements for Non-CTIMPs</td>
<td><a href="http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/">http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/</a></td>
</tr>
<tr>
<td>NRES Guidance on Safety Reports for Non-CTIMPs</td>
<td><a href="http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-">http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-</a></td>
</tr>
</tbody>
</table>
## Non-Interventional Studies

Under the Medicines for Human Use (Clinical Trials) Regulations 2004 ([SI 2004/1031](https://www.legislation.gov.uk/ukpga/2004/1031/contents)) it is not a legal requirement to obtain either clinical trial authorisation or a favourable opinion from an ethics committee to conduct such trials.

Where such trials are considered to be research and involve NHS patients or their tissue or data, they do require ethical review in the same way as other research undertaken in or
through the NHS (as per Section 2.2.2 of the Department of Health’s Research Governance Framework for Health and Social Care, 2005).

Definitions

(1) “clinical trial” means any investigation in human subjects, other than a non-interventional trial, intended—

   a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
   b) to identify any adverse reactions to one or more such products, or
   c) to study absorption, distribution, metabolism and excretion of one or more such products,

with the object of ascertaining the safety or efficacy of those products;

As per Regulation 2 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)

(2) “non-interventional trial or study” means a study of one or more medicinal products which have a marketing authorization, where the following conditions are met—

   a) the products are prescribed in the usual manner in accordance with the terms of that authorization,
   b) the assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a protocol but falls within current practice,
   c) the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study,
   d) no diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of the particular therapeutic strategy in question, and
   e) epidemiological methods are to be used for the analysis of the data arising from the study;

As per Regulation 2 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and Clause 13.1 of the ABPI COP.
Prospective Non-interventional Studies of Marketed Products

According to the applicable UK regulations, guidelines and the ABPI COP, non-interventional studies that are prospective in nature and involve the collection of patient data must comply with the following criteria:

**Purpose**

NIS must be conducted for a scientific purpose (Clause 13.3 of the ABPI COP).

**Prohibition of Promotion**

The study must not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine (Clauses 13.3 and 20 of the ABPI COP).

Market research activities, clinical assessments, post-marketing surveillance and experience programmes, post-authorisation studies (including those that are retrospective in nature) and the like must not be disguised promotion. They must be conducted with a primarily scientific or educational purpose (Clause 12.2 of the ABPI COP).

Market research is the collection and analysis of information and must be unbiased and non-promotional. The use to which the statistics or information is put may be promotional. The two phases must be kept distinct (as per the Supplementary Information for Clause 12.2 of the ABPI COP).

Attention is drawn to the Legal & Ethical Guidelines for Healthcare Market Research produced by the British Healthcare Business Intelligence Association in consultation with the ABPI (as per the Supplementary Information for Clause 12.2 of the ABPI COP).

Market research material should be examined to ensure that it does not contravene the Code (as per the Supplementary Information for Clause 12.2 of the ABPI COP).

Where market research is carried out by an agency on behalf of a pharmaceutical company, the agency must reveal the name of its client to the Prescription Medicines Code of Practice Authority when the Authority requests it to do so. When commissioning market research, a company must take steps to ensure that its identity would be so made known to the Authority should a request for that information be made (as per the Supplementary Information for Clause 12.2 of the ABPI COP).
Scientific Service (Body Responsible for Approval & Supervision of NIS)

The Company’s Scientific Service must approve the protocol and must supervise the conduct of the study (Clause 13.3 of the ABPI COP).

Companies must have a Scientific Service to deal with the approval and supervision of non-interventional studies. The Scientific Service must include a registered Medical Practitioner or, where appropriate, a pharmacist, who will be responsible for the oversight of non-interventional studies (including the review of any responsibilities relating to such studies, particularly those given to Medical Representatives). That person must state in writing that he or she has examined the protocol relating to the non-interventional study and that in his or her belief it is in accordance with the requirement of the ABPI COP (as per Clauses 13.3 and 21.2 of the ABPI COP).

Limited Involvement of Sales Reps

Sales Representatives may only be involved in an administrative capacity and such involvement must be under the supervision of the Company’s Scientific Service which will also ensure that the representatives are adequately trained for the role; such involvement must not be linked to the promotion of any medicine (Clause 13.3 of the ABPI COP).

Competent Authority Approval

Non-interventional trials do not require authorisation by, or notification to, the MHRA†††††††††††† (MHRA Website - Clinical trial authorisations: Is a clinical trial authorisation required?).

Favourable Ethics Opinion

In countries where Ethics Committees are prepared to review such studies, the study protocol must be submitted to the Ethics Committee for review (Clause 13.3 of the ABPI COP).

In the UK, the favourable opinion from an NHS research ethics committee (REC) is required before starting a non-interventional study (as per the NRES SOPs and Section 2.2.2 of the Department of Health Research Governance Framework).

* Further clarified by a personal email received from the MHRA Clinical Trials Helpline on 16th Oct 2009.
There are two classifications of clinical research acknowledged by NRES, clinical trials of investigational medicinal products (CTIMPs) and all other clinical research (Non-CTIMPs). Non-interventional studies fall in the category of Non-CTIMP.

**Ethical Review Application to be Submitted by the Chief Investigator**

An application for ethical review of a research study should be made by the Chief Investigator for that study. Applications may not be submitted by the sponsor(s) on behalf of the Chief Investigator. The Chief Investigator should normally be professionally based in the United Kingdom. For international studies with a co-ordinating investigator outside the UK, a health professional based in the UK should normally be nominated as the Chief Investigator responsible for the conduct of the research in the UK. The REC may agree exceptionally to an application being submitted by a CI based outside the UK but should consider as part of the ethical review whether adequate arrangements are in place for supervision of the study in the UK (as per Paragraph 1.1 of NRES SOP, Version 5, Sept 2011).

**On-Line Application Tool (IRAS)**

All new applications for ethical review to a Research Ethics Committee (REC) in the UK should be submitted on the standard on-line REC application form in the Integrated Research Application System (IRAS) ([http://www.myresearchproject.co.uk](http://www.myresearchproject.co.uk)) (as per Paragraph 1.4 of NRES SOP, Version 5, Sept 2011).

**Non-interventional Trials**

Trials of medicinal products which are “non-interventional” are not classified as clinical trials of investigational medicinal products (CTIMPs) by the UK RECs and therefore do not require review by a recognised REC. Instead, they should be allocated for REC review in accordance with the normal procedures for non-CTIMPs (Paragraph 1.24 of NRES SOP, Version 5, Sept 2011).

**Determining whether a study is a CTIMP or a Non-CTIMP**

The MHRA has published guidance on the interpretation of the statutory definition of a CTIMP and a non-interventional trial (see algorithm at Annex F of NRES SOP). Where there is doubt about the classification of a trial, it is the responsibility of the Chief Investigator or sponsor to seek authoritative advice from the MHRA Clinical Trials Helpline, using the
contact details on the MHRA website (as per Paragraph 1.25 of NRES SOP, Version 5, Sept 2011).

The REC should proceed with the ethical review but advise the applicant of the possible consequences if the application has been wrongly classified. The applicant may be required to provide written evidence from the MHRA as part of the single request for further information (see Section 3). Where the MHRA advises that an application submitted as a non-CTIMP is in fact a CTIMP, the application should be withdrawn and re-submitted with a EudraCT number and the additional information required. Where a study is submitted as a non-CTIMP and given a favourable opinion, and it emerges later that it is in fact a CTIMP, corrective procedures are set out in paragraph 5.3 of Annex D (as per Paragraph 1.25 of NRES SOP, Version 5, Sept 2011).

Non-Interventional Trials Involving Adults Lacking Capacity to Consent

Only one application for ethical review should be submitted in relation to any research protocol to be conducted within the UK (except where two applications are required for non-CTIMPs involving adults lacking capacity in both England/Wales and Scotland – see paragraph 12.57 of NRES SOP, Version 5, Sept 2011) (as per Paragraph 1.2 of NRES SOP, Version 5, Sept 2011).

Non-Interventional Trial/Research Project or Audit?

Some projects within the definition of a "non-interventional trial" might be deemed not to be research at all, but rather clinical audit, service evaluation or some other type of non-research activity such as post-market surveillance. If so, they would not require ethical review by a NHS REC or permission for research under the Research Governance Framework for Health and Social Care; the NHS care organisation will have other procedures in place for agreeing to activity of this kind, for example review under clinical governance frameworks. The NRES leaflet, "Defining Research", provides guidance on distinguishing between research, audit and service evaluation.

Within the NHS and social care services, the responsibility for determining whether a project should be managed as research under the Research Governance Framework lies with the responsible R&D office. Requests for pre-application advice should be referred initially to the R&D office, or a lead R&D office in the case of a project involving multiple organisations. The R&D office may itself seek further advice from a REC or the NRES Queries Line, or recommend that the sponsor or project team seeks such advice, by submitting a brief outline of the project in writing. Where a REC receives such a request, it should be referred
to the Chair, who is encouraged to provide advice but is not obliged to do so. Where the Chair is available and willing to advise, a response should be sent within 5 working days using SL24. Otherwise, the correspondent should be referred to the NRES Queries Line (as per Paragraph 1.94 of NRES SOP, Version 5, Sept 2011).

Where an application is made to a REC, i.e. the project is presented as research, it should be validated and reviewed in the normal way if the research is within the scope of REC review under GAfREC. If the REC considers that the project should not have been presented as research, it may give advice alongside its opinion that the status of the project is reconsidered by the sponsor in consultation with the lead R&D office. If the sponsor or project team subsequently notifies that the REC that the application is no longer considered to be research, the application and opinion letter should be considered to be withdrawn (as per Paragraph 1.95 of NRES SOP, Version 5, Sept 2011).

**Allocation of non-CTIMPs**

Trials of medicinal products which are “non-interventional” (see definition in the Glossary) are not classified as CTIMPs and do not require review by a recognised REC. They should be allocated in accordance with the normal procedures for non-CTIMPs (as per Paragraph 1.24 of NRES SOP, Version 5, Sept 2011).

**NRES Forms for use by applicants (non-CTIMPs)**

- Notice of substantial amendment (NRES Website Link)
- Declaration of the end of a study and final report (NRES Website Link)
- Annual progress report form (NRES Website Link)
- Report of serious adverse event (NRES Website Link)

All forms are issued by NRES and can be downloaded from the NRES Website.

**Management Permission**

Is required from the organisation responsible for hosting the research before it commences at any site (Paragraph 4.6 of NRES SOP, Version 4, April 2009).
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 research activities must be formally approved by Trust management before starting.

Studies performed in NHS hospitals will require permission/approval from the relevant R&D Trust before starting the study. Such permission can now be sought using the UK’s integrated research application system (IRAS).

**Contract & Protocol**

There must be a written protocol and written contracts between the Health Professionals and/or the institutes at which the study will take place and the pharmaceutical company sponsoring the study, which specify the nature of the services to be provided and the payment for those services (Clause 13.3 of the ABPI COP).

Health Professionals may be used as consultants and advisors for services such as involvement in medical/scientific studies (e.g., NIS), clinical trials etc. The arrangements which cover these genuine consultancy or other services must, to the extent relevant to the particular arrangement, fulfil the following criteria (Clause 20.1 of the ABPI COP):

- a written contract or agreement must be agreed in advance of the commencement of the services which specifies the nature of the services to be provided and the basis for the payment of those services

- A legitimate need for the services must be clearly identified in advance of requesting the services and entering into arrangements with the prospective consultants

- The criteria for selecting consultants must be directly related to the identified need and the persons responsible for selecting the consultants must have the expertise necessary to evaluate whether the particular health professionals meet those criteria

- The number of health professionals retained must not be greater than the number reasonably necessary to achieve the identified need

- The contracting company must retain records concerning, and make appropriate use of, the services provided by consultants

- The hiring of health professionals to provide the relevant service must not be an inducement to prescribe, supply, administer, recommend, buy or sell any medicine
The compensation for the services must be reasonable and reflect the fair market value of the services provided. In this regard, token consultancy arrangements must not be used to justify compensating health professionals.

**Model Agreements**

Nationally approved standard agreements help speed up the contracting process for clinical trials carried out in the NHS. The agreements are part of a system of reforms to streamline the process of conducting clinical trials in the NHS, as part of the NIHR goal of creating a world class clinical research environment.

Up by the UK Health Departments, the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA), and the Association for British Healthcare Industries (ABHI), as appropriate, and endorsed for use in unmodified format by representatives of the NHS and universities.

Refer to the [Model Clinical Trials Agreements](#).

Currently, there is no model agreement, which is specific to non-interventional studies. Sponsors may be asked by host institutions to use the model clinical trials agreement (mCTA) and should consider the relevance of such an agreement given that much of the content of the template/agreement will be irrelevant to NIS. A letter of intent or similar contract may be more appropriate for these types of studies.

Further guidance is provided on the Department of Health website: [Model Clinical Trial Agreements](#).

**Financial Compensation/Remuneration**

Any remuneration must be reasonable and reflect the fair market value of the work (Clause 13.3 of the [ABPI COP](#)).

**Declaration of Fees Paid to Consultants**

Pharmaceutical companies must make publicly available details of the fees paid to consultants in the UK, or to their employers on their behalf, for certain services rendered by them such as chairing and speaking at meetings, assistance with training and participation in advisory boards etc. It does not include payments to consultants in relation to research and development work, including the conduct of clinical trials. Nor does it include payment of
UK travel costs or the cost of subsistence in relation to fees for services which are dealt with in Clause 20.3 (as per Clause 20.2 of the ABPI COP).

In addition to the information required to be made public by Clause 20.2, companies must make publicly available details of payments made to consultants in relation to market research (unless the company concerned is not aware of the identities of those participating in the market research) and payments in respect of accommodation (both in and outside the UK) and travel outside the UK in relation to fees for services as defined in Clause 20.2 (as per Clause 20.3 of the ABPI COP).

Fees, expenses and the like due to consultants in relation to Clauses 20.2 and 20.3 must be declared whether paid directly to them or to their employers or to companies or charities etc (as per Clause 20.4 of the ABPI COP).

**Insurance and Indemnity**

Before confirming a favourable opinion on any research (including both CTIMPs and non-CTIMPs), the main REC should assure itself that the sponsor and investigators will have appropriate insurance or indemnity cover for the potential legal liability arising from the research, and consider provision in proportion to the risk for compensation or treatment in the event of injury, disability or death attributable to participation. Detailed guidance is in Annex G (as per Paragraph 3.56 of NRES SOP, Version 5, Sept 2011).

**Compliance with Data Protection Legislation**

Data protection legislation must be complied with (Clause 13.3 of the ABPI COP).

**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.
For further information, refer to the following:

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

Registration of Clinical Studies

Companies must publish the summary details and results of non-interventional studies of marketed medicines in a manner consistent with their parallel obligations with respect to clinical trials (Clause 13.2 of the ABPI COP)

Investigator Meetings (Meetings, Hospitality and Sponsorship)

Companies must not provide hospitality to members of the health professions and appropriate administrative staff except in association with scientific meetings, promotional meetings, scientific congresses and other such meetings, and training. Meetings must be held in appropriate venues conducive to the main purpose of the event. Hospitality must be strictly limited to the main purpose of the event and must be secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which the recipients would normally adopt when paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff (Clause 19.1 of the ABPI COP).

Payments may not be made to doctors or groups of doctors or to other prescribers, either directly or indirectly, for rental for rooms to be used for meetings (Clause 19.2 of the ABPI COP).

When meetings are sponsored by pharmaceutical companies, that fact must be disclosed in all of the papers relating to the meetings and in any published proceedings. The declaration of sponsorship must be sufficiently prominent to ensure that readers are aware of it at the outset (Clause 19.3 of the ABPI COP).

Pharmaceutical companies must make publicly available financial details of sponsorship of UK health professionals and appropriate administrative staff in relation to attendance at meetings organised by third parties. Sponsorship in this context includes registration fees,
costs of accommodation (both inside and outside the UK) and travel outside the UK (Clause 19.4 of the ABPI COP).

**Progress Reports**

The Chief Investigator should submit a progress report to the relevant Research Ethics Committee (REC) 12 months after the date on which the favourable REC opinion was given. Annual progress reports should be submitted thereafter (NRES Annual Progress Report Form [NRES Website Link]).

**Substantial Amendments**

If it is proposed to make a substantial amendment to the research, the Chief Investigator should submit a notice of amendment to the relevant REC.

A substantial amendment is any amendment to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the REC, that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial participants

(b) the scientific value of the trial

(c) the conduct or management of the trial

Notices of amendment should be in the format prescribed by NRES and published on the website, and should be personally signed by the Chief Investigator. The agreement of the sponsor should be obtained before submitting the notice of a substantial amendment.

- NRES Notice of Substantial Amendment Form ([NRES Website Link])

For non-CTIMPs, the same definition of a “substantial amendment” as for CTIMPs applies and a favourable opinion from the main REC is always required before implementation (as per Section 5 of [NRES SOP], Version 5, Sept 2011).

The policy of the UK Health Departments is that the statutory provisions relating to substantial amendments to CTIMPs should generally apply to the review of substantial amendments to any research study that has previously been ethically approved by a REC. There will however be some procedural differences, which are indicated in this section. The 35 day clock applies to review of all substantial amendments, except those proposing to include adults lacking capacity for the first time in a non-CTIMP, where 60 days is allowed.
for the review and the clock may be stopped once to request further information or clarification (see paragraph 12.61) (as per paragraph 5.8 of NRES SOP, Version 5, Sept 2011).

A substantial amendment should not be implemented until a favourable ethical opinion has been given by the Committee, unless the changes to the research are urgent safety measures. The REC is required to give an opinion within 35 days of the date of receiving a valid notice of amendment (Annex C, Paragraph 5 of NRES SOP, Version 4, April 2009).

Amendments that are not substantial amendments (“minor amendments”) may be made at any time and do not need to be notified to the Committee (Annex C, Paragraph 5 of NRES SOP, Version 4, April 2009).

Is my Amendment Substantial?

In a clinical trial of an investigational medicinal product (CTIMP), the legal responsibility to decide whether an amendment is substantial lies with the trial sponsor. Guidance is available from the European Commission:

- Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, notification of substantial amendments and declaration of the end of the trial (2010/C 82/01) (Revision 3 of March 2010)

In all other research, the Research Ethics Committee that gave a favourable opinion (the ‘main REC’) has the discretion to decide whether or not a proposed amendment is substantial and requires ethical review. Chief investigators and sponsors should seek advice from the main REC if in doubt.

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.

For further information refer to the NRES Guidance on Notification of Amendments

Safety Reporting for Non-CTIMPs

In research other than CTIMPs, a Serious Adverse Event (SAE) is defined as an untoward occurrence that:

a) Results in death;
b) Is life-threatening;

c) Requires hospitalisation or prolongation of existing hospitalisation;

d) Results in persistent or significant disability or incapacity;

e) Consists of a congenital anomaly or birth defect; or

f) Is otherwise considered medically significant by the investigator.


An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

- “Related” – that is, it resulted from administration of any of the research procedures, and

- “Unexpected” – that is, the type of event is not listed in the protocol as an expected occurrence.


Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the NRES website (as per Paragraph 9.68 of NRES SOP, Version 5, Sept 2011).

The Chief Investigator should include a report on the safety of participants in the annual progress report (as per Paragraph 9.69 of NRES SOP, Version 5, Sept 2011).

Individual reports of SAEs should be reviewed at a sub-committee or Committee meeting (as per Paragraph 9.70 of NRES SOP, Version 5, Sept 2011).

There is no requirement to provide reports to RECs other than the main REC (as per Paragraph 9.71 of NRES SOP, Version 5, Sept 2011).

Refer to the following NRES webpage for further information and relevant submission forms:

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

End of Trial Notifications
The policy from NRES is that the requirement to notify the main REC of conclusion or early termination should also apply to all other research with a favourable opinion. In the case of non-CTIMPs, reports should be submitted in the form prescribed by NRES and published on the website (as per Paragraph 9.83 of NRES SOP, Version 5, Sept 2011).

The Clinical Trials Regulations provide that the sponsor should notify the MHRA and the main REC in writing that a CTIMP has ended within 90 days of the conclusion of the trial. In the case of an international trial, guidance from the European Commission is that the sponsor is only required to notify the conclusion of the trial as a whole. Where the UK arm of a trial ends in advance of the conclusion in all Member States, this may be notified voluntarily (the form for declaring the end of the trial should not be used in this case) (as per Paragraph 9.79 of NRES SOP, Version 5, Sept 2011).

If the trial is terminated early, the sponsor should notify the main REC within 15 days of the date of termination. An explanation of the reasons for early termination should be given (as per Paragraph 9.80 of NRES SOP, Version 5, Sept 2011).

The definition of the conclusion of the research should be provided in the protocol and any change to this definition should be notified as a substantial amendment. The end of the research should be defined in relation to the collection of all data required to answer the research questions in the protocol. Where a clinical trial protocol requires follow-up monitoring and data collection to meet secondary or tertiary endpoints, the end of trial should be the final data capture rather than the last treatment visit (as per Paragraph 9.81 of NRES SOP, Version 5, Sept 2011).

The Chief Investigator should notify the Committee in writing that the research has ended within 90 days of its conclusion. The conclusion of the research is defined as the final date or event specified in the protocol, not the completion of data analysis or publication of the results.

If the research is terminated early, the Chief Investigator should notify the Committee within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

Reports of conclusion or early termination should be submitted in the form prescribed by NRES and published on the website:

- NRES Declaration of the End of a Study and Final Report Forms (NRES Website Link)

Analysis and Retention of Study Results
The study results must be analysed and summaries must be made available within a reasonable period to the Company’s Scientific Service, which shall maintain records of such reports (Clause 13.3 of the ABPI COP).

Dissemination of Summary Reports

The summary report should be sent to health professionals who participated in the study (Clause 13.3 of the ABPI COP).

A summary of the final report on the research should be provided to the relevant REC within 12 months of the conclusion of the study. This should include information on whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination of the research including any feedback to participants should be submitted in the form prescribed by NRES and published on the website:

- NRES Declaration of the End of a Study and Final Report Forms (NRES Website Link)

Notification of Important Benefit-Risk Information

If the study results are important for the assessment of benefit-risk, the summary report should be immediately forwarded to the relevant competent authority (Clause 13.3 of the ABPI COP).

According to paragraph 10(d) of Schedule 3 of The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 (SI 1994/3144):

Any person who, while employed or engaged as an appropriately qualified person responsible for pharmacovigilance for the purposes of Chapter 3 of Title II of Council Regulation (EEC) No. 2309/93, or Title IX of the 2001 Directive fails to:

(i) in post authorization safety studies;

(ii) in a country which is not an EEA State;

(iii) outside the terms of the marketing authorization, including use in clinical trials as defined in Article 2(a) of the Clinical Trials Directive (2001/20/EC).

As required by any provision of any such Chapter or Title, shall be guilty of an offence.

Other Non-interventional Studies of Marketed Products

According to the supplementary information which has been provided for Clause 13 in the ABPI COP:

“Companies are encouraged to comply with Clause 13.3 (Criteria for prospective NIS) for all other types of studies covered by Clause 13.1, including epidemiological studies and registries and other studies that are retrospective in nature.”

Useful Links

Data Protection Links

| The Information Commissioner's Office | http://www.ico.gov.uk/ |
UK Competent Authority (Clinical Trials)

Medicines and Healthcare products Regulatory Agency (MHRA)

Accessed From:
http://www.mhra.gov.uk/index.htm

MHRA Algorithm: Is it a Clinical Trial of a Medicinal Product or a Non-Interventional Clinical Trial?

Accessed From:

MHRA Publication: The Blue Guide – Advertising and Promotion of Medicines in the UK (2005)

Accessed From:
http://www.mhra.gov.uk/home/groups/pla/documents/websiteresources/con007552.pdf

UK Ethical Review Process

National Research Ethics Service (NRES)

Accessed From:
http://www.nres.npsa.nhs.uk/

NRES Guidance on Ethical Review Requirements

Accessed From:
http://www.nres.npsa.nhs.uk/applications/approval-requirements/ethical-review-requirements/

Integrated Research Application System (IRAS)

Accessed From:
https://www.myresearchproject.org.uk/

NRES Guidance on IRAS

Accessed From:
http://www.nres.npsa.nhs.uk/applications/integrated-research-application-system/

NRES Standard Operating Procedures (Version 5.0, September 2011)

Accessed From:

NRES Guidance: After ethical review - guidance for sponsors and investigators (research other than CTIMPs) (v4.0, September 2011)

Accessed From:
http://www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=11397

NRES Guidance on Annual Progress Report Requirements for Non-CTIMPs

Accessed From:
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

NRES Guidance on Safety Reports for Non-CTIMPs

Accessed From:
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

NRES Guidance on Notification of Amendments

Accessed From:
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/notification-of-amendments/

NRES Guidance on End of Study and Final Report Requirements

Accessed From:
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/

EFGCP Report: UK (April 2011)

Accessed From:
UK Legislation & Guidelines (Relating to Non-Interventional Studies)

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)
- Refer to the CHCUK GCP Regulatory Maps for an up to date summary of the amendments to SI 2004/1031


The Medicines Act 1968 (as updated in applicable statutory instruments)

NRES Guidance on IRAS

NRES Standard Operating Procedures (Version 5.0, September 2011)

NRES Guidance: After ethical review - guidance for sponsors and investigators (research other than CTIMPs) (v4.0, September 2011)

NRES Guidance on Annual Progress Report Requirements for Non-CTIMPs

NRES Guidance on Safety Reports for Non-CTIMPs

NRES Guidance on Notification of Amendments

NRES Guidance on End of Study and Final Report Requirements

Accessed From:


http://www.nres.npsa.nhs.uk/applications/integrated-research-application-system/


http://www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=11397

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/notification-of-amendments/

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/
### UK Legislation & Guidelines (Relating to Non-Interventional Studies)

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### UK Pharmaceutical Industry Self-regulatory Body

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<td>Association of British Pharmaceutical Industries (ABPI)</td>
<td><a href="http://www.abpi.org.uk/Pages/default.aspx">http://www.abpi.org.uk/Pages/default.aspx</a></td>
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Pharmaceutical Advertising


- Refer specifically to Section 5.4: Is it possible to pay doctors to provide expert services (e.g. participating in focus groups)? If so, what restrictions apply?

- Refer Specifically to Section 5.5: Is it possible to pay doctors to take part in post marketing surveillance studies? What rules govern such studies?

Accessed From: http://www.iclg.co.uk/index.php?area=4&country_results=1&kh_publications_id=197&chapters_id=4594