# GCP Considerations: The Investigator's Brochure (IB)

## Guidance on the Purpose, Design and Management of an Investigator's Brochure (IB): EU & UK


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# Document History

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# Guidance on the Purpose, Design and Management of an Investigator's Brochure (IB): EU & UK

# The Investigator's Brochure: UK Considerations

## Regulatory Overview

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|---|---|
| **Competent Authority:** | Medicines and Healthcare products Regulatory Agency (MHRA) |
| **Research Ethics Committees (RECs):** | National Research Ethics Service (NRES)<br>(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) |

## 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).

## The Investigator's Brochure (IB)

### What is an Investigator's Brochure?

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects (as per Section 7.1 of ICH E6).

**Implemented into law through:**

**EU:** Article 2(g) of 2001/20/EC

**UK:** Regulation 2 of SI 2004/1031

### What is the purpose of an IB?

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

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

**Implemented into law through:**

**EU:** Article 8.1 of 2005/28/EC

**UK:** Regulation 3A(a) of SI 2004/1031 (as amended by SI 2006/1928)

### How Should the Information be Presented?

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data (as per Section 7.1 of ICH E6).


**Implemented into law through:**

**EU:** Article 8.1 of 2005/28/EC

**UK:** Regulation 3A(a) of SI 2004/1031 (as amended by SI 2006/1928)

## What Information Should be Included in the IB?

Refer to Section 7 of ICH E6, which clearly describes the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product (as per Section 7.1 of ICH E6).

**Implemented into law through:**

**EU:** Article 4 of 2005/28/EC

**UK:** Schedule 1, Part 2.8 of SI 2004/1031 (as amended by SI 2006/1928)

## What if the Investigational Product is Marketed, do I Still Need an IB?

If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that might be of importance to the investigator (as per Section 7.1 of ICH E6).

If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared (as per Section 7.1 of ICH E6).

The approved Summary of Product Characteristics (SmPC) will replace the IB if the IMP is authorised in any MS, and it is used according to the terms of the marketing authorisation. But when the conditions of use in the CT differ from those authorised, the SmPC should be complemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial (as per Section 2.6 of ENTR/CT1).

In practical terms, this means that:


(1) Where the investigational medicinal product has a marketing authorization and the product is to be used in accordance with the terms of that authorization, the summary of product characteristics relating to that product should be used, or

(2) Where the investigational medicinal product has a marketing authorization and the product is not being used in accordance with the terms of that authorization, the summary of product characteristics should be complemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in that clinical trial. Alternatively, this may be addressed through the use of the Investigator's Brochure relating to that product.

Refer to Table 1 for further details.

**Implemented into law through:**

**EU:** Articles 2, 3.3, 8.1, 8.3(j) & 11 of 2001/83/EC (as amended)

**EU:** Article 8.2 of 2005/28/EC

**UK:** Regulation 15(5)(e) and Part 1.3(b) of Schedule 3 of SI 2004/1031 (as amended by SI 2006/1928)

## How Often Should I Review and Update an IB?

The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly the IRBs/IECs and/or regulatory authorities before it is included in a revised IB (as per Section 7.1 of ICH E6).

**Implemented into law through:**

**EU:** Article 8.3 of 2005/28/EC

**UK:** Regulation 3A(b) of SI 2004/1031 (as amended by SI 2006/1928)

## What Happens if I Don't Comply with these Requirements?

This is decided upon, and implemented at, the national level within Europe. In the UK, the defining regulation is The Medicines for Human Use (Clinical Trials) Regulations, 2004 (SI


2004/1031) which has since been updated and amended by SI 2006/1928, SI 2006/2984, SI 2008/941, SI 2009/1164, and SI 2010/1882.

➔ Refer to the CHCUK GCP Regulatory Map for a more detailed and comprehensive overview of the amendments to, and impact on, the Medicines for Human Use (Clinical Trials) Regulations, 2004

According to Regulation 49 of SI 2004/1031 (as amended), any person who contravenes Regulation 3A (Sponsor's responsibility for the investigator's brochure) will be guilty on an offence. The penalties for committing such an offence are listed under Regulation 52 and include a fine or imprisonment from between 3 months and 2 years depending on the nature and severity of the offence.

However, Regulation 51 does introduce an element of pragmatism and provides for the "defence of due diligence" which when demonstrated would mean that although the requirement(s) had been contravened, an offence wasn't committed as all reasonable precautions and all due diligence had been exercised to avoid commission of that offence.

## Useful Links

### Global Guidelines

- ICH E6 - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Good Clinical Practice E6 (R1)
    - Commonly referred to as 'ICH GCP'
    - Also referred to as the Community guideline on Good Clinical Practice (CPMP/ICH/135/95)

### European Directives & Guidelines

- 2001/83/EC (as amended) - Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use
- 2001/20/EC - Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use


- 2005/28/EC - 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

- Eudralex Volume 10 - Eudralex Volume 10 (Clinical Trials Guidelines) of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

- ENTR/CT1 - Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial, October 2005

**UK Competent Authority**

- Medicines and Healthcare products Regulatory Agency (MHRA)
    - MHRA's Good Clinical Practice (GCP) Inspectorate

**UK Regulations**

- 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
        - SI 2010/1882 - The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010
    - Refer to the CHCUK GCP Regulatory Maps for a current summary of the amendments to SI 2004/1031
    - Refer also to the resource available from Canary Ltd which presents the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments


in a single easy to use consolidated document: [The UK Clinical Research Regulations: Consolidated and Indexed]


**Table 1 - Guidance on the Source of Medicinal Product Information to be provided to Investigators for Authorised/ Registered Medicinal Products**

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

| Scenario | IMP-Related Reference Information for Investigator | Legal Basis | Comments |
|---|---|---|---|
| IMP which is not registered/ marketed but is authorised to be investigated in humans | Investigator's Brochure | ▪ ICH E6 (Section 7.1)<br>▪ 2001/20/EC (Article 2d & 2g)<br>▪ ENTR/CT1 (Section 2.6)<br>▪ SI 2004/1031 (Regulation 15.5.e & Schedule 3, Part 1.3.b) | |
| Registered/ authorised IMP to be investigated in Humans. To be used or assembled (formulated or packaged) in a way different from the authorised form, or to be used for an unauthorised indication, or to be used to gain further information about the authorised form | (1) Investigator's Brochure, | ▪ ICH E6 (Section 7.1)<br>▪ 2001/20/EC (Article 2d & 2g)<br>▪ SI 2004/1031 (Regulation 15.5.e & Schedule 3, Part 1.3.b) | |
| | (2) Investigator's Brochure complemented with an SmPC | ▪ No References Found | |

| Scenario | IMP-Related Reference Information for Investigator | Legal Basis | Comments |
|---|---|---|---|
| | | | |
| | (3) SmPC complemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial | ▪ 2005/28/EC (Article 8.2)<br>▪ ENTR/CT1 (Section 2.6) | The UK law (SI 2004/1031) makes no allowance for the either/or scenario discussed here. If the IMP is used within the scope of the marketing authorisation then the use of the SmPC is permitted. If used outside of the authorised scope, then an IB should be used.<br><br>ENTR/CT3 adds further clarification when discussing which documents an investigator should refer to in assessing the expectedness of an ADR :<br>▪ the investigator's brochure for non-authorised investigational medicinal product<br>▪ the summary of product characteristics for an authorized medicinal product in the European Community, which is being used according to the terms and conditions of the marketing authorization |

| Scenario | IMP-Related Reference Information for Investigator | Legal Basis | Comments |
|---|---|---|---|
| | | | |
| Registered/ authorised IMP to be investigated in Humans in accordance with the marketing authorisation. | Summary of Product Characteristics (SmPC) or equivalent (e.g., product label in USA) | ▪ 2005/28/EC (Article 8.2)<br>▪ ENTR/CT1 (Section 2.6)<br>▪ ENTR/CT3 (Section 4.2.5)<br>▪ SI 2004/1031 (Regulation 15.5.e & Schedule 3, Part 1.3.b) | |

***For the UK, if in doubt, contact the MHRA:***

1. E-mail info@mhra.gsi.gov.uk
2. Website: MHRA's Good Clinical Practice (GCP) Inspectorate

**REFERENCES**

2001/20/EC - DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use


2005/28/EC - 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

ENTR/CT1 - Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), March 2010

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

ICH E6 - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Good Clinical Practice E6 (R1)

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
    - SI 2010/1882 - The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010
- Refer to the CHCUK GCP Regulatory Maps for a current summary of the amendments to SI 2004/1031


- Refer also to resource available from Canary Ltd which provides the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments in a single easy to use document: The UK Clinical Research Regulations: Consolidated and Indexed


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