Clinical Trial Authorisations and MHRA Inspections

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Outline

• Background
• What is a clinical trial?
• Current regulations governing clinical trials
• GCP
• CTA applications
• MHRA inspections
The importance of a competent authority

1958-1960: Europe – thalidomide synthetic compound triggered review of practice leading to Declaration of Helsinki 1964

2001: Healthy volunteer dies at Johns Hopkins University after taking part in asthma trial

March 2006: Parexel catastrophe at Northwick Park Hospital

2007: Various convictions for counterfeit medicines

2008: EU suspension of Acomplia (rimonabant)
Drug Testing Process

**Lab Testing**
- Tissue samples
- Computer simulation
- In vitro tests
- Animal testing
- Tests for toxicity
- MHRA & ethics
- IMP ok for humans

**Human Testing**

**Phase 1:** Healthy volunteers
- Testing for safety, PK and PD, tolerability

**Phase II:** Selected people with relevant illness
- Testing for clinical efficacy

**Phase III:** Large number of people with relevant illness
- Testing against “gold standard”

**Post Marketing**

**Phase IV:** Post surveillance. Wider testing against other drugs, testing for further side effects and long-term risks and benefits
Definition of IMP

“Investigational Medicinal Product" is a pharmaceutical form of an active substance or placebo being tested or used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial:

– used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
– used for an indication not included in the summary of product characteristics under the authorisation for that product, or
– used to gain further information about the form of that product as authorised under the authorisation;
What is a clinical trial? MHRA algorithm

**IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?**

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

| Is it a medicinal product (MP)?
| Is it not a medicinal product?
| What effects of the medicine are you looking for?
| Why are you looking for those effects?
| How are you looking for those effects? |
|---|---|---|---|---|
| A | B | C | D | E |
| **A CLINICAL TRIAL OF A MEDICINAL PRODUCT?** | **A NON-INTERVENTIONAL CLINICAL TRIAL?** |
| If you answer no to all the questions in column A, the activity is not a clinical trial on a MP. | If you answer yes to the question below in column B the activity is not a clinical trial on a MP. | If you answer no to all the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC. | If you answer no to all the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC. | If you answer yes to all these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. |
| If you answer yes to any of the questions below go to column C. | If you answer yes to any of the questions below go to column C. | If you answer yes to any of the questions below go to column D. | If you answer yes to any of the questions below go to column E. |

A.1 **Is it a substance** or combination of substances presented as having properties for treating or preventing disease in human beings?

A.2 **Does the substance function as a medicine?**

i.e. Can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?

A.3 **Is it an active substance in a pharmaceutical form?**

B.1 **Are you only administering any of the following substances?**

- Human whole blood
- Human blood cells
- Human plasma
- Tissues except a somatic cell therapy medicinal product
- A food product (including dietary supplements) not presented as a medicine
- A cosmetic product
- A medical device

C.1 **To discover or verify/compare its clinical effects?**
C.2 **To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?**
C.3 **To identify or verify/compare its adverse reactions?**
C.4 **To study or verify/compare its absorption, distribution, metabolism or excretion?**

D.1 **To ascertain or verify/compare the efficacy of the medicine?**
D.2 **To ascertain or verify/compare the safety of the medicine?**

E.1 **Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?**
E.2 **Are the products prescribed in the usual manner in accordance with the terms of that authorisation?**
E.3 **Does the assignment of any patient involved in the study to a particular therapeutic strategy fail within current practice and is not decided in advance by a clinical trial protocol?**
E.4 **Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?**
E.5 **Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?**
E.6 **Will epidemiological methods be used for the analysis of the data arising from the study?**
What is a Clinical Trial? Simplified

• Is it a medicinal product?
  – e.g. is the substance presented as a medicine or used to make a medical diagnosis?

• What effects of the medicine are you looking for?
  – e.g. clinical, pharmacological effects

• Why are you looking for those effects?
  – e.g. efficacy or safety

• Is it non-interventional?
  – e.g. routine therapy, epidemiological methods, only current practice diagnostic or monitoring procedures.

Email: clintrialhelpline@mhra.gsi.gov.uk
Current Regulations Governing Clinical Trials

• UK Medicines for Human Use (Clinical Trials) Regulations 2004
  – 1 May 2004
  – Amended August 2006: EU GCP Directive
  – Amended December 2006: Emergency research
  – Amended May 2008: Children in emergency research

• 2005 Research Governance Framework for Health and Social Care

• Human Tissue Act (2004)

• Public access database

(Mental Capacity Act (2005))
2001/20/EC: EU Clinical Trials Directive

• EU Clinical Trials Directive 2001/20/EC came into UK law as Medicines for Human Use (Clinical Trials) Regulation
2005/28/EC EU Good Clinical Practice Directive

• The GCP Directive supplements the EUCTD

• Requires Member States to comply with the principles and guidelines of ICH GCP
Principles of GCP

1. Ethical Principles of Declaration of Helsinki
2. Benefit justifies risk
3. Rights, safety, wellbeing
4. Adequate information to support trial
5. Clear, scientifically sound protocol
6. Favourable ethics approval
7. Qualified Chief Investigator
8. Researcher training, education and experience
9. Freely given informed consent
10. Accurate data handling and storage
11. Data Protection and confidentiality
12. Good Manufacturing Practice
13. Quality assurance systems
Clinical Trial Authorisation (CTA)

• The basics:
  – Register on EudraCT Database (http://eudract.emea.europa.eu/)
  – Prior to/or parallel with Ethics Application
  – Fee: Phase I, II, III known product
  – Should respond within 30 days

• For guidance, refer to:
  http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice/standardoperatingprocedures
Clinical Trial Application Menu

EudraCT Number: 2006-002134-37
Sponsor’s Protocol Code Number: cro111
Member State Competent Authority: UK - MHRA

NOTE: The system will ‘timeout’ if there is a period of inactivity. For this reason, and to avoid accidental data loss you must 'Save as XML' to your local computer (or other accessible drive) at the start of the session and regularly thereafter. This is because no data is stored by the EudraCT system except temporarily during the current session.
The 'Continue' button is used during data entry, this does NOT store your information on disk; it only preserves the information within your current application form.
On the screens accessed via the links below, ▲ indicates the item is part of the core data set as per the Annex to the Detailed Guidance ENTR/CT 5 describing the core data set.

A. Trial Identification
B. Sponsor Identification
C. Applicant Identification
D. Information on the IMPs
D.7. Information on the Placebos
D.8. Site(s) where the qualified person certifies batch release
E. General Information on the Trial
F. Population of Trial Subjects
G. Clinical Trial Sites/ Investigators in the Member State
H. Ethics Committee/ MS Competent Authority
FAQs – B: Sponsor Details

<table>
<thead>
<tr>
<th>B.1 and B.3 Sponsor Identification Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>EudraCT Number: 2006-002134-37</td>
</tr>
<tr>
<td>Sponsor's Protocol Code Number: c0111</td>
</tr>
<tr>
<td>Member State Competent Authority: UK - MHRA</td>
</tr>
<tr>
<td>Reference ID: SP1</td>
</tr>
</tbody>
</table>

These are the details for section B.1 and B.3 Sponsor Identification Details. Enter details, and use 'Continue'.

- **B.1.1 Name of organisation**: Imperial College
- **B.1.2 Contact person**
  - **Given name**: Gary
  - **Middle name**: Roper
  - **Family name**: 
- **B.1.3 Street address**
  - **Town/ city**: 602, Sir Alexander Fleming Bull
  - **Post code**: SW7 2AZ
  - **Country**: UNITED KINGDOM
- **B.1.4 Telephone number**: 020 7594 1188
- **B.1.5 Fax number**: 020 7594 1792
- **B.1.6 E-mail address**: gary.roper@imperial.ac.uk

For section B.2, first complete B.3 below then select 'Continue' and then add a legal representative if required by Article 19 of Directive 2001/20/EC.

- **B.3.1 and B.3.2 Status of the sponsor**: Non-Commercial

A commercial sponsor is a person or organisation that takes responsibility for a trial which is part of the development programme for a marketing authorisation of a medicinal product at the time of the application.

As on A59 NRES / A64 IRAS of ethics application
FAQs – C: Applicant Identification

C.1 Applicant Identification - Request for the Competent Authority

| EudraCT Number: 2006-002134-37 |
| Sponsor's Protocol Code Number: cro111 |
| Member State Competent Authority: UK - MHRA |

These are the details for section C. Applicant Identification. Enter details, and use 'Continue'.

This is the Applicant to the MS Competent Authority. Enter the details of the legal Applicant (who will sign the form). The Contact Name may be a different individual at the same Location/Organisation. The Phone, Fax and E-mail should be those of the Contact person.

C.1.1 and C.1.2 and C.1.3
A person or organisation authorised by the sponsor

C.1.4 Complete the details of the applicant below even if they are provided elsewhere on the form.

C.1.4.1 Person or organisation name
Clinical Research Office
Patricia
C.
Henley

C.1.4.2 Name of person to contact - Given name
G02, Sir Alexander Fleming Buil
London
SW7 2AZ
UNIVERSITY KINGDOM
020 7594 1893

Complete for Both MS Competent Authority AND Ethics
FAQs – D: IMP Details

D. IMP Identification Index

Click ‘add IMP’ to start the first IMP or create another one. Once an IMP is added, links for ‘edit’, ‘delete’, ‘copy’, ‘search MPD to add active’ and ‘add active substance’ are displayed for that IMP. Use ‘search MPD to add active’ to find and create an active substance from the list of available active substances in the Medical Product Dictionary (MPD). Use ‘add active substance’ for all active substances in that IMP.

Complete all questions in Section D for each IMP, but if most of the answers are the same for any additional IMP(s) (e.g., 3 tablets of different strength), then enter one IMP, use the ‘copy IMP’ function on this screen, then edit the relevant fields in the copy.

<table>
<thead>
<tr>
<th>ID</th>
<th>Details</th>
<th>edit</th>
<th>delete</th>
<th>search MPD to add active</th>
<th>add active substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3</td>
<td>Erbitux/Erlotinib/n/a/L01XC06/Intravenous Infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS3</td>
<td>CETUXIMAB/IC/Erlotinib/mg/kg milligram(s)/kilogram</td>
<td>edit</td>
<td>delete</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CETUXIMAB/205923564/ based on MPD record: SUB01178MIG on 2006-06-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR4</td>
<td>Xeloda/Xeloda/n/a/L01BC/Tablet</td>
<td>edit</td>
<td>delete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS4</td>
<td>IC/CAPECITABINE/1300/mg/kg milligram(s)/kilogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From supplier, IB or SmPC
## FAQs – D8: QP Site

### D.8 Index of Sites where the qualified person certifies batch release

<table>
<thead>
<tr>
<th>EudraCT Number</th>
<th>2006-002134-37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor's Protocol Code Number</td>
<td></td>
</tr>
<tr>
<td>Member State Competent Authority</td>
<td>UK - MHRA</td>
</tr>
</tbody>
</table>

This records the Sites responsible for final QP Release for distribution to Investigators for the IMPS selected 'Yes' in the following screen(s).

- **D.8.1** list IMPs and placebos for which no responsible site needs to be identified

- **D.8.2** add responsible site

<table>
<thead>
<tr>
<th>ID</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Responsible Sites have been added for this application</td>
<td></td>
</tr>
</tbody>
</table>

Application Menu Page

### Manufacturer/Importer details
FAQs – D8.1

D.8.1 IMPs and placebos for which no responsible site needs to be identified

EudraCT Number: 2006-002134-37
Sponsor's Protocol Code Number: cro111
Member State Competent Authority: UK - MHRA

This section is used to identify IMPs and placebos which:

- Have an MA in the EU and
- Are sourced from the EU market and
- Are used in the trial without modification (e.g., not overencapsulated) and
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2003/28/EC (GCP Directive).

If all the conditions above are met, then tick this box ✓ ▲ and select below the IMPs and placebos to which this applies.

Finished IMP

<table>
<thead>
<tr>
<th>PR3</th>
<th>Erbitux/Erbilux/n/a/L01x06</th>
</tr>
</thead>
</table>

Finished IMP

<table>
<thead>
<tr>
<th>PR4</th>
<th>Xeloda/Xeloda/n/a/L01BC</th>
</tr>
</thead>
</table>


FAQs – D8.2 QP Site

D.8 Site where the qualified person certifies batch release

EudraCT Number : 2006-002134-37
Sponsor’s Protocol Code Number : cro111
Member State Competent Authority : UK – MHRA
Reference ID :

This section is dedicated to finished IMPs, i.e., medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified then give each IMP its number from section D.1.1 or D.7.2. In the case of multiple sites indicate the product certified by each site.

Note that section D.8.1 relates to IMPs that do not need to have responsible sites identified. This section of the form can be accessed from screen "D.8 Index of Sites where the qualified person certifies batch release" by selecting the option ‘D.8.1 list IMPs and placebos for which no responsible site needs to be identified’.

This is a multi-screen form; use the navigation key 'Next' to navigate to each of the screens. IMP and Placebo responsibilities are on the next screen.

D.8.2 Who is responsible in the Community for the certification of the finished IMPs?

Note that the identification of IMPs and placebos is on the next screen. Complete sections D.8.2.1 to D.8.2.4.1 below first and then select ‘Next’ to identify the IMPs and placebos released by this site.

D.8.2.1 and D.8.2.2

As a manufacturer, importer or both? ▲

D.8.2.3

Site organisation name ▲

D.8.2.3.1

Street address

Town/ city ▲

Post code

Country ▲
FAQs – E: MedDRA

Use search tool for Code
FAQs – G3: Central Technical Facilities

EudraCT Number : 2006-002134-37
Sponsor’s Protocol Code Number : cro111
Member State Competent Authority : UK - MHRA
Reference ID : CTF1

Only central facilities should be completed who supply services for at least this Member State. The facility may be in this Member State, another Member State or a 3rd Country.

<table>
<thead>
<tr>
<th>G3.1 Organisation</th>
<th>Blood Analysis co</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central technical facility organisation name</td>
<td></td>
</tr>
<tr>
<td>Central technical facility organisation department</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G3.2 Contact person - Given name</th>
<th>Bram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle name</td>
<td></td>
</tr>
<tr>
<td>Family name</td>
<td>Stoker</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G3.3 Street address</th>
<th>Blood ODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Town/ city</td>
<td>Transylvania</td>
</tr>
<tr>
<td>Post code</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>ROMANIA</td>
</tr>
</tbody>
</table>

e.g. central lab analysis or IMP re-encapsulation or IMP distribution
FAQs – G4

G.4 Organisations to whom the sponsor has transferred trial related duties and functions

EudraCT Number : 2006-002134-37
Sponsor’s Protocol Code Number : cro111
Member State Competent Authority : UK - MHRA
Reference ID :

Only central CRO facilities supplying services for at least this Member State should be entered (not e.g. individual field-based CRAs). The facility may be in this Member State, another Member State or a 3rd Country.

Note that the answer to question ‘G.4.1 Has the sponsor transferred any major or all the sponsor’s trial related duties and functions to another organisation or third party will be filled in automatically by the system once the details of the first subcontractor have been entered.

G.4.1.1 Organisation name

G.4.1.2 Contact person - Given name

G.4.1.4 Telephone number

Enter the details of any duties/ functions subcontracted to this sponsor’s subcontractor facility in this trial:

- G.4.1.5 All tasks of the sponsor
- G.4.1.6 Monitoring
- G.4.1.7 Regulatory (e.g. preparation of applications to CA and Ethics Committee)
- G.4.1.8 Investigator recruitment
- G.4.1.9 IVRS - treatment randomisation
- G.4.1.10 Data management
- G.4.1.11 E-data capture
- G.4.1.12 SUSAR reporting
- G.4.1.13 Quality assurance auditing
- G.4.1.14 Statistical analysis
- G.4.1.15 Medical writing
- G.4.1.16 Other Duties subcontracted?
   - G.4.1.16.1 If ‘Yes’, specify the other duties

Continue  Cancel
What type of IMPD should be submitted?

• Full IMPD
  – IMPs without MA in any Member State
  – IMPs where MHRA have not granted CTA previously
  – IMPs where relevant information can not be cross-referred

• Simplified IMPD
  – IMPs assessed previously in any Member State or as CTA to MHRA
  – May require letter of cross-referral to the data submitted by other applicant

• SmPC
  – Marketed products
Responses from the MHRA

• Acceptance

• Acceptance with remarks
  – Similar to ethics provisional approval
  – Mandatory to respond to remarks
  – MHRA will send acknowledgement letter

• Notice of non-acceptance
  – Will inform you of points to amend
  – Reply within 15 days otherwise will need to complete new CTA
MHRA – Inspections

Types of inspections:

• **Good Clinical Practice**
  – Fee: Approx £5000 per day for 2 inspectors
• Good Manufacturing Practice
• Good Distribution Practice
• Good Laboratory Practice
• Good Pharmacovigilance Practice
MHRA – Inspections

• “Back to Basics” Inspection model:
  – Are all approvals in place?
    • SI 2004:1031, Part 3 Regulation 12(1) and (3)
  – How GCP compliant is the trial?
    • SI 2004:1031, Part 4 Regulation 28
  – Is safety information being captured?
    • SI 2004:1031, Part 4 Regulations 32, 33 and 35
  – Have relevant bodies been notified of trial end?
    • SI 2004:1031, Part 3 Regulation 27 parts (1) to (3); Schedule 3, Part 4 (5)
MHRA – Inspections

What they are looking for:

- Contract Management
- Project Management
- Monitoring
- Pharmacovigilance
- Data management
- Statistical analysis
- IMP management
- TMF management

- Regulatory submissions
- Quality assurance
- Training
- Computer systems
- Report writing
- Archives
- Laboratories
- Selected site visit
Definition of Findings

Findings rated as:
• Critical
  – Critical findings referred to CTIAG: MHRA Clinical Trials Inspection Action Group
• Major
• Other

Consequences of Non-compliance
• Infringement notices: EEA States and RECs
• Criminal Offences:
  – Contravene Regulations
  – Provide false or Misleading information
• Penalties
  – **Fine or Prison Sentence**
MHRA – Inspections: Common Findings 1

• Contracts, Agreements, Insurance
  – Contract not in place
  – Inconsistency between protocol & contract
  – Insurance exemptions not covering patient population

• Missing, out of date or poorly controlled SOPs

• Poor safety reporting

• Inadequate investigator participation – excessive and/or inappropriate delegation of duty
MHRA – Inspections: Common Findings 2

• Inadequate consent procedures
  – No consent record, incorrect form used

• IMP: missing documentation

• Poor understanding of GCP requirements
  – Free training!

• Violation of protocol – happens regularly!

• Poor maintenance of source documents & database protected access
Process Map

EXTERNAL FUNDING
Non-Commercial Sponsor
e.g. CTIMP in UK/EU, any other
UK research in the NHS

Which approvals are needed based on the protocol?

NHS R&D Initial Consultation

Regulatory Approvals, if required (excluding ethics)
e.g. MHRA, PIAG, HFEA

Clinical Research Office Approval
(Insurance Confirmation / Sponsor Assessment)

Ethics Approval

Internal Div. / Dept. Approval

Research Services Approval

Submit Application / Contract Signed

Final NHS R&D Approval

Register on public database (if required)

Initiate Study

Have all College / ethics / regulatory approvals and funding been received?
Useful Guidance

- MHRA – how to submit a CTA

- EudraCT – website for CTA application

- Eudralex volume 10 (EU guidance on running clinical trials)

- Clinical Trials Toolkit
  - [http://www.ct-toolkit.ac.uk/](http://www.ct-toolkit.ac.uk/)
Summary

• The Clinical Trials Regulations are:
  – Standardised
  – Best Practice &
  – Here to stay!

If in doubt - check with Clinical Research Governance Office
m.quaye@imperial.ac.uk
Lucy.parker@imperial.ac.uk
www.ic.ac.uk/clinicalresearchgovernanceoffice
Statistic Advisory Service

Course: Introduction to Design and Analysis of Clinical Trials

- [http://www3.imperial.ac.uk/stathelp/courses/introductiontodesignandanalysisofclinicaltrials](http://www3.imperial.ac.uk/stathelp/courses/introductiontodesignandanalysisofclinicaltrials)

- **Richard** on 0207 594 3856 or [r.kells@imperial.ac.uk](mailto:r.kells@imperial.ac.uk)

- Next Course: Thur 23 & Fri 24 April