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.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A CLINICAL TRIAL OF A MEDICINAL PRODUCT?</strong></td>
<td><strong>A NON-INTERVENTIONAL CLINICAL TRIAL?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is it a medicinal product (MP)?</td>
<td>Is it not a medicinal product?</td>
<td>What effects of the medicine are you looking for?</td>
<td>Why are you looking for those effects?</td>
<td>How are you looking for those effects?</td>
</tr>
<tr>
<td>If you answer no to all the questions in column A, the activity is not a clinical trial on a MP.</td>
<td>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</td>
<td>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.</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>If you answer yes to any of the questions below go to column B.</td>
<td>If you answer no to this question below go to column C.</td>
<td>If you answer yes to any of the questions below go to column D.</td>
<td>If you answer yes to any of the questions below go to column E.</td>
<td></td>
</tr>
<tr>
<td><strong>A.1 Is it a substance or combination of substances presented as having properties for treating or preventing disease in human beings?</strong></td>
<td><strong>B.1 Are you only administering any of the following substances?</strong></td>
<td><strong>C.1 To discover or verify/compare its clinical effects?</strong></td>
<td><strong>D.1 To ascertain or verify/compare the safety of the medicine?</strong></td>
<td><strong>E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?</strong></td>
</tr>
<tr>
<td>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?</td>
<td>• 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</td>
<td>• To discover or verify/compare its clinical effects?</td>
<td>• To ascertain or verify/compare the safety of the medicine?</td>
<td><strong>E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation?</strong></td>
</tr>
<tr>
<td>A.3 Is it an active substance in a pharmaceutical form?</td>
<td></td>
<td>• To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?</td>
<td></td>
<td><strong>E.3 Does the assignment of any patent involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol?</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To identify or verify/compare its adverse reactions?</td>
<td></td>
<td><strong>E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To study or verify/compare its absorption, distribution, metabolism or excretion?</td>
<td></td>
<td><strong>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?</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>E.6 Will epidemiological methods be used for the analysis of the data arising from the study?</strong></td>
</tr>
</tbody>
</table>
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
- Public access database

(Mental Capacity Act (2005))
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
Where do I add in the IMP details?

- NHS REC Form
- NHS/HEC R&D Form (project information)
- MHRA Medicines (EudraCT application form)
### EudraCT Application Form

**Application to:** Medicines and Healthcare products Regulatory Agency (MHRA) - Medicines

### Project Forms

- NHS REC Form
- NCB/HPF R&D Form (project information)
- MHRA Medicines (EudraCT application form)

### Site-specific Forms

No SSI Forms created yet.

### Navigate

<table>
<thead>
<tr>
<th>MHRA Medicines - EudraCT Form Navigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Print blank reference only PDF for this form</td>
</tr>
</tbody>
</table>

### Status

- enabled
- disabled

<table>
<thead>
<tr>
<th>SUB-SECTION</th>
<th>QUESTION RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Trial identification</td>
<td>A1-A2</td>
</tr>
<tr>
<td>B. Sponsor</td>
<td>B1</td>
</tr>
<tr>
<td>C. Application</td>
<td>C1</td>
</tr>
<tr>
<td>D. Information on the IMPs</td>
<td>D</td>
</tr>
</tbody>
</table>

### Medicinal Products

- IMP = PR1

| D7. Information on the Placebos  | D7             |
| D8. Site(s) where the qualified person certifies batch release | D8             |
| E. General information on the trial | E1 | E2 | E3-E5 | E6-F7 | E8 |
| F. Population of Trial Subjects  | F1-F3 | F4-F6 |
| G. Clinical Trial Sites/Investigators in the Member State | G1-G2 | G3 | G4 |
| H. Ethics Committee/ National Competent Authority | H1-H4 |
| I. Signature of the applicant in the member state | I1-I2 |
| J. Checklist of Information      | EudraCT Checklist |
FAQs – B: Sponsor Details

B: Identification of the sponsor responsible for the request

B1. Sponsor

<table>
<thead>
<tr>
<th>SP1 Contact person</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of organisation</td>
<td>Imperial College London</td>
</tr>
<tr>
<td>Given name</td>
<td>Lucy</td>
</tr>
</tbody>
</table>

| Family name | Parker |
| Address |  |
| Town/city |  |
| Post code |  |
| Country |  |
| Telephone |  |
| Fax |  |
| E-mail |  |

B2. Legal representative in the European Economic Area for the purpose of this trial

A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal Representative 1
FAQs – C: Applicant Identification

C1. Request for the competent authority

C1.1. Who is responsible for the Clinical Trial Authorisation Application?

Person or organisation authorised by the Sponsor

C1.4. Complete the details of the applicant below even if they are provided elsewhere on the form:

Contact person

Person or organisation name: Joe Smith

Contact person Given name

Contact person Family name

Address

Town/city

Post code

Country

Telephone

Fax

E-mail
FAQs – D: IMP Details

D: Information on the IMPs

Information on each “bulk product” before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable. If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.

Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the “See All” link and return to this section to enter details of the next product. When you have completed details of all products please move to question D7 using the navigation screen.

D. Investigational medicinal products

<table>
<thead>
<tr>
<th>PR1</th>
<th>Xeloda</th>
</tr>
</thead>
</table>

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

#### D8. Sites responsible for final QP release for distribution to investigators.

**D8.1. IMPS and placebos for which no responsible site needs to be identified.**

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 2005/56/EC (GCP Directive).

If all the conditions above are met, then select below the IMPS and placebos to which this applies.

- Add IMP
- Add Placebo

**Index of Sites where the qualified person certifies batch release**

In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medicinal Products in the European Union.

**D8.2. Who is responsible in the Community for the certification of the finished IMP or placebo?**

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, use extra pages and give each IMP its number from section D1 or D7. In the case of multiple sites indicate the product certified by each site.
FAQs – D8.1

D8.1. IMPs and placebos for which no responsible site needs to be identified.

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 (eg not overencapsulated) and
- The packaging and labelling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive)

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

Add IMP

Placebo PL1

Add Placebo
D8.2. Who is responsible in the Community for the certification of the finished IMP or placebo?

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, use extra pages and give each IMP its number from section D1 or D7. In the case of multiple sites, indicate the product certified by each site.

RS1

- Importer
- Manufacturer
- Both

Address

Town/city
Post code
Country

Give the manufacturing authorisation number

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.
IMP Documentation

- Summary of Product Characteristics (SmPC)
- Investigators Brochure (IB)
- Investigational Medicinal Product Dossier (IMPD)
- MA(IMP)
- QP Declaration
### G3. Central technical facilities to be used in the conduct of the trial

Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised.

**CTF-1**

<table>
<thead>
<tr>
<th>Organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central technical facility organisation name</strong></td>
</tr>
<tr>
<td><strong>Central technical facility organisation department</strong></td>
</tr>
<tr>
<td><strong>Contact person Given name</strong></td>
</tr>
<tr>
<td><strong>Contact person Family name</strong></td>
</tr>
<tr>
<td><strong>Street address</strong></td>
</tr>
<tr>
<td><strong>Town/city</strong></td>
</tr>
<tr>
<td><strong>Post code</strong></td>
</tr>
</tbody>
</table>

**Country**

| **Work Telephone** |  |

**Enter the details of any duties subcontracted to this central technical facility in this trial:**

| Routine clinical pathology testing |  |
| Clinical chemistry |  |
| Clinical haemostology |  |
| Clinical microbiology |  |
| Histopathology |  |
| Serology / endocrinology |  |
| Analytical chemistry |  |

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

#### G4. Organisations to whom the sponsor has transferred trial related duties and functions

**G4. Has the sponsor transferred any major or all the sponsor’s trial related duties and functions to another organisation or third party?**

- [ ] Yes
- [ ] No

**Subcontractor organisations.**

*Enter details of central CRO facilities supplying services for at least this Member State.*

<table>
<thead>
<tr>
<th>TMF1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organisation</strong></td>
<td>Perfect Monitoring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Department</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact person Given name</td>
<td>Greta</td>
</tr>
<tr>
<td>Contact person Family name</td>
<td>Smith</td>
</tr>
<tr>
<td>Street address</td>
<td></td>
</tr>
<tr>
<td>Town/city</td>
<td></td>
</tr>
<tr>
<td>PostCode</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>Telephone number</td>
<td></td>
</tr>
</tbody>
</table>

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

- All tasks of the sponsor:
  - [ ] Yes
  - [ ] No
- Monitoring:
  - [ ] Yes
  - [ ] No
# CTA Submission Documents

<table>
<thead>
<tr>
<th>Documents to be provided for CTA submission to MHRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. General</strong></td>
</tr>
<tr>
<td>1.1 Receipt of confirmation of EudraCT number</td>
</tr>
<tr>
<td>1.2 Covering letter</td>
</tr>
<tr>
<td>1.3 Application form (xml &amp; pdf)</td>
</tr>
<tr>
<td>1.4 List of Competent Authorities within the Community which the application has been submitted and details of decisions</td>
</tr>
<tr>
<td>1.5 Copy of Ethics Committee opinion in the MS concerned when available</td>
</tr>
<tr>
<td>1.6 Copy/summary of any scientific advice</td>
</tr>
<tr>
<td>1.7 If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor²</td>
</tr>
<tr>
<td><strong>2. Protocol Related</strong></td>
</tr>
<tr>
<td>2.1 Clinical trial protocol with all amendments to date</td>
</tr>
<tr>
<td><strong>3. IMP Related</strong></td>
</tr>
<tr>
<td>3.1 Investigator’s brochure</td>
</tr>
<tr>
<td>4.2 Investigational Medicinal product dossier (IMPD)²</td>
</tr>
<tr>
<td>4.3 Simplified IMPD for known products²</td>
</tr>
<tr>
<td>4.4 Summary of Product Characteristics (SmPC) (for products with marketing authorisation within the EC)²</td>
</tr>
<tr>
<td>4.5 Outline of all active trials with the same IMP</td>
</tr>
<tr>
<td>4.6 If IMP manufactured in EU and if no marketing authorisation in EU</td>
</tr>
<tr>
<td>4.6.1 Copy of the manufacturing authorization referred to in Art 13.1 of the Directive stating the scope of the authorisation</td>
</tr>
<tr>
<td>4.7 If IMP not manufactured in EU and if no marketing authorisation in EU</td>
</tr>
<tr>
<td>4.7.1 Certification of the GP that the manufacturing site works in compliance with GMP, at least equivalent to EU GMP, or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality</td>
</tr>
<tr>
<td>4.7.2 Certification of GMP status of active biological substance</td>
</tr>
<tr>
<td>4.7.3 Copy of the importer’s manufacturing authorization referred to in Art 13.1 of the Directive stating the scope of this authorization</td>
</tr>
<tr>
<td>4.8 Certificate of Analysis for test product in exceptional cases</td>
</tr>
<tr>
<td>4.8.1 Where impurities (not covered by the specification) are detected</td>
</tr>
<tr>
<td>4.9 Viral studies (where applicable)</td>
</tr>
<tr>
<td>4.10 Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMO, radiopharmaceuticals</td>
</tr>
<tr>
<td>4.11 TSE certificates (when applicable)</td>
</tr>
<tr>
<td>4.12 Examples of the label in the national language</td>
</tr>
</tbody>
</table>
How to Submit CTA Application

• Fee should be sent with application
• Electronic submission only
• Specific structuring and naming of documents on disc
• Disc must be labelled correctly

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/MakingclinicaltrialssubmissionstotheMHRA/index.htm
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
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/
Summary

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

If in doubt - check with Joint Research Office
m.quaye@imperial.ac.uk
Lucy.parker@imperial.ac.uk
www.ic.ac.uk/clinicalresearchgovernanceoffice