http://www.mhra.gov.uk/PrintPreview/DefaultSplashPP/CON071400?ResultCount=10&DynamicListQuery=&DynamicListSortBy=xCreationDate&DynamicListSortOrder=Desc&DynamicListTitle=&PageNumber=1&Title=Applying%20to%20conduct%20a%20clinical%20trial%3A%20Additional%20information

Preparing your application

IMPD
IB
Protocol

Application form

The first step in an application is to obtain a EudraCT number. This is a unique identifier which is required for all trials conducted with an investigational medicinal product in any EU Member State. It can only be obtained from the EudraCT pages of the EMA website (external link).

The application form can then be completed and downloaded using either the Integrated Research Application System (IRAS) (external link) or the EudraCT website (external link). Once completed the clinical trial application form should be saved as an EudraCT XML file.

Signatures

The signature page of the application form must be signed for inclusion on the disk. Either insert a signature image into the Word document (eg copy image 'Paste Special>Picture [Windows metafile]') prior to conversion to PDF, or print, sign, scan and then merge the signature page with the relevant PDF. Please note that digital signatures are currently not accepted.

XML file

An XML file is the data format of the saved clinical trial application form information. It is created via the IRAS (external link) or the EudraCT website (external link). The XML file of the completed clinical trial application form information is required to enable us to enter the details of the trial into the EudraCT website (external link), as we are obliged to do by the Clinical Trials Directive 2001/20/EC.

IMP Dossier

An IMP dossier should accompany each application. On a case by case basis, this may be a full dossier or a simplified dossier. Information on when a simplified dossier can be used is available:

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 (external link).

Information on the content of the IMP dossier can be found on the EMA website:

Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link)

Points to consider when preparing the IMP dossier

Analytical validation

Sections 2.2.1.S.4.3 and 2.2.1.P.5.3 of the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) require that a tabulated summary of the results of the validation of analytical methods used in the control of the drug substance and drug product is included in the IMP dossier. There is no requirement for the inclusion of a full validation report. This should not be provided.

Batch analysis data

Sections 2.2.1.S.4.4 and 2.2.1.P.5.4 of the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) require the provision of representative batch analysis data. Batch analysis data for each company listed in the IMP dossier as a proposed site of manufacture for drug substance and for drug product should be provided. In this context, a company is regarded as a legal entity. In the same way, a substantial amendment supported by batch analysis data will have to be submitted and approved prior to the inclusion of manufacturing sites which represent a new company (legal entity). For biological and biotechnological products, batch analysis data will be required for each site of manufacture.

Retest period

Section 2.2.1.S.7 of the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) requires the provision of stability data summarised in a tabular format. To ensure that the drug substance complies with its specification at the time of manufacture of the drug product, a re-test period based on the available stability data should be included in the IMP dossier. Extrapolation may be used in the setting of the re-test period. Where the drug substance continues to meet its approved specification and where the proposed re-test period is matched by acceptable real time stability data, no substantial amendment will be required to extend the re-test period. These provisions also apply to setting the shelf life for a biological and biotechnological drug substance.

Shelf life Section

2.2.1.P.8 of the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) requires that a shelf life based on available stability data be set. Extrapolation may be used. Where an acceptable shelf life extension plan is included in the IMP dossier, no substantial amendment will be required to extend the shelf life of the drug product. For products coming within the scope of the 'Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials', an acceptable shelf life extension plan should comprise the following elements:

- specification against which the product is tested

- criteria used to extrapolate data
- analysis of trends
- proposed extension based on available real time data and acceptable accelerated data – this should not exceed four times the available real-time data to a maximum of 12 months or 12 months plus the available real-time data, ie:

Three months real-time data	12 months shelf life
Six months real-time data	18 months shelf life
12 months real-time data	24 months shelf life
24 months real-time data	36 months shelf life

The same principles can be applied to biological and biotechnological products where an acceptable shelf life extension plan should comprise the following elements:

- specification against which the product is tested
- proposed extension based on available real time data.

IMP dossier design
Where an IMP comprises multiple strengths of the product, only one IMP dossier is required. This should cover all strengths of the product. The provision of one dossier per product strength is not required.

Labelling
The Commission's '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' requires the submission of trial labelling as part of the application for a clinical trial authorisation.

Where a sponsor wishes to claim an exemption from the need for trial specific labelling under the provisions of Regulation 46 of SI 2004 No 1031, a statement to this effect has to be included in the application. This file should be named following the requirements for naming the file containing the labelling sample [4.12 Label].
Where labelling is revised after the clinical trial authorisation is approved, this may constitute a substantial amendment. However, there is no requirement for the prior submission and approval of a substantial amendment where the change is to alter the particulars of items in the approved labelling eg a new expiry date or a change in sponsor name or where the change is repositioning of the components of an approved

label.

Manufacturer's authorisation

The manufacture and/or assembly (packaging and labelling) of an investigational medicinal product can only be undertaken by the holder of an authorisation for the manufacture of investigational medicinal products. A copy of the manufacturer's authorisation should be provided for each EU site undertaking any manufacturing step in the preparation of the test product or any comparator. Blinding of a comparator product by over encapsulation is manufacture.

This requirement to hold a manufacturer's authorisation does not apply in the following situations:

1. the manufacture or assembly is in accordance with the terms and conditions of a marketing authorisation relating to that product
2. the assembly is carried out in a hospital or health centre by a doctor, a pharmacist or a person acting under the supervision of a pharmacist; and the investigational medicinal products are assembled exclusively for use in that hospital or health centre, or any other hospital or health centre which is a trial site for the clinical trial in which the product is to be used.

Where manufacture and/or assembly occur outside of the EU, the product has to be imported by the holder of a manufacturer's authorisation covering the activity of importation of IMPs. A copy of the manufacturer's authorisation should be provided as part of the application. In addition, a copy of the QP declaration on GMP equivalence to EU GMP should be provided.

A template for this declaration is available:

Qualified Person declaration concerning investigational medicinal products manufactured in third countries (27Kb)

The QP declaration is usually signed by a QP named on the manufacturer's authorisation of the importer but may be signed by a QP at the batch release site if this is different. In such cases, a copy of the manufacturer's authorisation for the batch release site is also required. The QP declaration is trial and product specific.

Investigator's brochure

An investigator's brochure is part of the CTA application. This should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product (IMP) in the trial and be presented in the format of summaries. The summary of product characteristics (SmPC) will replace the investigator's brochure if the IMP is authorised in any EU Member State and it is used according to the terms of the marketing authorisation. When the conditions of use in the clinical trial differ from those authorised, the SmPC should be complemented with a summary of relevant data that support the use of the IMP in the clinical trial. This can be provided as an investigator's brochure or, in some cases, may be incorporated into the protocol.

Points to consider when preparing the investigator's brochure:

- when the IMP is identified in the protocol only by its active substance, the sponsor should elect one SmPC as equivalent to the investigator's

brochure for all medicinal products that contain that active substance and are used at any clinical trial site
- for an international trial where the medicinal product to be used in each member state is the one authorised at a national level and the SmPC varies among member states, the sponsor should chose one SmPC to replace the investigator's brochure for the whole clinical trial
- the current investigator's brochure or equivalent document (eg SmPC for marketed products) will be the reference document for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.

Protocol

The content and format of the protocol should comply with the guidance in the community guideline on Good Clinical Practice (CPMP/ICH/135/95) (external link). The version submitted should include all currently authorised amendments and a definition of the end of the trial. It should be identified by the title, a sponsor's code number specific for all versions of it, a number and date of version that will be updated when it is amended, and by any short title or name assigned to it, and be signed by the sponsor and principal investigator (or co-ordinating investigator for multicentre trials).

Points to consider when preparing the protocol:

- the evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20 should be included in the protocol along with a justification for including subjects who are incapable of giving informed consent, or other special populations
- an important part of the protocol is the justification for the inclusion of trial participants based on gender and reproductive status. In addition, the protocol should include the contraceptive requirements for trial participants - Clarification of contraceptive wording in clinical trials
- where there is the potential for effects on the QT interval, the protocol should include specific inclusion/exclusion criteria, appropriate monitoring and relevant stopping criteria Regulatory requirements for QT interval assessment (external link)
- a protocol may include a sub-study to be conducted at all trial sites or only at specific sites. The covering letter should draw attention to any sub-studies and information should be provided in Section F.2 of the application form and all other applicable sections and supporting documents.

After submission

Validation

The CTA will be validated on receipt and an acknowledgement letter will be sent to the

person submitting the application. This is the person named in section C of the clinical trial application form. If the application is valid then the assessment period will begin. This starts from the date of receipt of a valid application. If the application is not valid then the person making the application will be told of the deficiencies. A new application containing all the necessary components should be provided. Please note that we will not retain a copy of this submission. Invalid submissions will be confidentially destroyed.

Common errors seen at validation

15% of applications fail at the validation step. The most frequent causes of an application being considered invalid are listed below:

Failure to supply an XML file of the completed clinical trial application form:

The XML file of the completed clinical trial application form information is required to enable us to enter the details of the trial into the EudraCT website, as we are obliged to do by the Clinical Trials Directive 2001/20/EC (external link).

Failure to complete section C1 of the clinical trial application form or section D1 of the notification of amendment form

Section C1 of the clinical trial application form and D1 of the notification of amendment form provide information on the person authorised by the sponsor to correspond with the MHRA on behalf of the sponsor. We need this information in order to be able to communicate with you.

Failure to provide PDF documents for the protocol, investigator's brochure, investigational medicinal product dossier (IMPD) and summary of product characteristics (SPC) (where appropriate) that have undergone optical character recognition (OCR)

PDF documents of the protocol, investigator's brochure, IMPD and SPC (where appropriate) should be created directly from Word or undergo Adobe Acrobat optical character recognition (OCR) at the time of creation. PDF document scanned images should not be provided as it is not possible to cut-and-paste data in this format. The OCR layer also supports text searching within the document and across the entire MHRA document store. For further information on OCR files and how to make them, please see Special mail 5: frequently asked questions (1934Kb)

Password protection on disks

We ask that you do not password protect documents or discs as we may not have the software to access your data even if you supply the password. We need this information in order to be able to process and assess your application.

Assessment

The initial assessment will be performed within 30 days. For the purposes of this calculation, the day of receipt of the application by the Clinical Trials Unit is day 0. Applications for Phase 1 healthy volunteer studies will be assessed and processed within an average of 14 days.

When the application has been assessed the applicant will be sent a letter informing them of:

1. acceptance of the request for a clinical trial authorisation or

2. acceptance of the request for a clinical trial authorisation subject to conditions or
3. grounds for non-acceptance of the request for a clinical trial authorisation.

Acceptance of the request for a clinical trial authorisation subject to conditions

It is possible that the outcome of the assessment is acceptance of the request with conditions applied. Where the conditions are met, no further action is required by the sponsor. It is not necessary to confirm that the conditions are met. Where the conditions are not met, the authorisation is not valid and the sponsor should submit a substantial amendment supported by the relevant documentation to make the necessary changes. Information on submitting a substantial amendment is available:

CTA amendments

Grounds for non-acceptance and right to amend request letter

If there are deficiencies or inadequacies in your application, you will receive a letter giving notice of grounds for non-acceptance and your right to amend the request. You may respond by making an amended request for a clinical trial authorisation to the MHRA.

This amended request should cover all the issues raised by the letter giving the grounds for non-acceptance. No additional changes will be accepted in an amended request. You should send amended requests for general medicinal products (Reg 18) or products with special characteristics (Reg 20) within 14 days of receiving the letter detailing the grounds for non-acceptance, unless otherwise agreed with the MHRA.

You should send amended requests for gene therapy, somatic cell therapy (including xenogenic cell therapy) or products containing genetically modified organisms (Reg 19) within 30 days of receiving the letter detailing the grounds for non-acceptance, unless otherwise agreed with the MHRA.

Please note: as of Monday 15 November, MHRA will be sending details of all Grounds for Non-Acceptance letters by email rather than fax.
The email address used will be the email provided for the applicant contact in section C1 of the application form.

Amended request to conduct a clinical trial

If the MHRA receives a valid amended request for a clinical trial authorisation, the request will be assessed and the applicant notified in writing of one of the following:

1. acceptance of the amended request
2. acceptance of the amended request subject to conditions
3. grounds for non-acceptance of the amended request.

Letters informing the applicant of the MHRA's decision relating to an amended request for a general medicinal product (Reg 18) or a product with special characteristics (Reg 20) will be sent by the MHRA within 60 days of us receiving the original valid application.

It has additionally been agreed that responses for phase 1 healthy volunteer studies will be assessed within an average of 14 days. Notification of the MHRA's decision relating to an amended request for a gene therapy, somatic cell therapy (including xenogenic cell therapy) product or products containing genetically modified organisms (Reg 19) will be sent within 90 days of us receiving the original application unless otherwise advised.

If an amended request is not made or amended request not accepted

If a valid amended request for a clinical trial authorisation is not received by the MHRA, or if the amended request is not acceptable, the application will be deemed to have been refused.
For general medicinal products (Reg 18) or products with special characteristics (Reg 20), the refusal will occur 60 days from the date of receipt of the original valid application. When this occurs, the MHRA will not send a notification letter.
For gene therapy, somatic cell therapy (including xenogenic cell therapy), tissue engineered products or products containing genetically modified organisms (Reg 19) where a valid amended request is not received, the application will be refused 90 days after the MHRA received the original valid application, unless otherwise advised.
If a sponsor wishes to proceed with an application which has been refused, a new full submission (using the same EudraCT number) will have to be made.

Common errors seen during assessment
A review of the reasons for grounds for non-acceptance comments was conducted during 2008. Of all letters sent to request further information, almost half were to request basic information which should have been included in the initial application.

The most common errors included:

- manufacturer's authorisation missing or clarification required
- labelling missing or requiring revision
- Qualified Person (QP) declaration required
- serious unexplained suspected adverse reaction (SUSAR)/adverse drug reaction (ADR) provisions missing from protocol
- protocol inaccuracies (not consistent with IB or SmPC)
- application form inaccuracies.

Common scientific reasons for issuing a grounds for non-acceptance letter included:

- protocol revisions with regard to:
  -
  - safety monitoring
  - contraception/lactating women/Women of childbearing potential
  - follow up provisions missing/insufficient
  - dose level or duration
- IMPD revisions with regard to:
  -
  - manufacture and control of placebo product
  - information on modifications to licensed products (eg encapsulation).

Mock applications
We have produced guidance which includes a mock application for a fictitious product

(198Kb). The information presented illustrates the quantity and level of detail expected where it is available.
A mock application for a fictitious biotechnology product (175Kb) is also available This is provided to give an indication of the type of information expected for a product of this type in early stage development.

Useful links

EudraCT: European Clinical Trials (external link)
Good Clinical Practice (GCP)
Good Laboratory Practice (GLP)
Good Manufacturing Practice (GMP)
Clinical trial toolkit (external link)
Gene Therapy Advisory Committee (GTAC) (external link)
National Research Ethics Service (NRES) (external link)
HSE Genetically modified organisms contained use (external link)
DEFRA Genetically modified organism deliberate release (external link)
The Administration of Radioactive Substances Advisory Committee (ARSAC) (external link)
ICH M3(R2) (external link)

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