

# Clinical trial authorization process: EU (UK)

The application process to perform a clinical trial in Europe takes place on a country-by-country basis. Thus, a sponsor must apply for approval in each country in which it intends to have study sites. While the processes are similar in most countries, there are slight differences and, in some cases, additional material must be submitted. For example, in many European countries, a sponsor must submit a copy of the insurance coverage obtained to cover the clinical study.

In this document, we present the process used in the UK as it is a recognized standard.

The regulatory authority that governs therapeutics in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA).

To file a clinical trial application in the UK, a sponsor must reside or have a legal representative in the EU.

## Major parts of a clinical trial application (CTA)

A clinical trial application consists of several major parts:

- **Covering letter:** This should contain EudraCT (European Clinical Trials Database) number, the title and number of the study protocol, and information on any special issues such as first-time use in humans, use of special populations, or unusual trial design.
- **Clinical trial application form:** The form is available from the EudraCT website.
- **Protocol:** The protocol should include an evaluation of the anticipated benefits and risks, a justification for including any subjects who may not be able to provide informed consent (if applicable), and a description of the plan to provide additional care once patients leave the study, if different from normal medical care.
- **Investigator's Brochure (IB) or Summary of Product Characteristics\* (SmPC):** The IB should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and safe use of the investigational product.
- **Investigational Medicinal Product-related data:** Include the Investigational Medicinal Product Dossier (IMPD). This contains summaries of information related to the quality, manufacture and control of the investigational product. It should include chemical, pharmaceutical and biological data, non-clinical pharmacology and toxicology data, previous clinical trial and human experience data, and overall risk and benefit assessment. In cases where the investigational product has a marketing authorization in another EU member state or it has been approved in another pharmaceutical form, the sponsor can provide an abbreviated IMPD.
- **XML file of the application form:** Provide the complete data set.
- **Applicable fee.**

\* provide the SmPC when a drug has been commercialized

The specific requirements for each country in the EU are outlined in a guidance document published by the European Commission.<sup>1</sup>

A sponsor is required to obtain a EudraCT number. EudraCT is a database of all clinical trials occurring in Europe. It is operated by the European Medicines Agency (EMA). A sponsor obtains a EudraCT number by accessing the site and completing a EudraCT application. For a clinical trial to be performed in multiple EU countries, only one EudraCT number is required.

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<sup>1</sup> European Commission Enterprise Directorate-General. (2005, October). *Detailed guidance for the request of 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*. Retrieved March 2, 2010, from [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11\\_ca\\_14-2005.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11_ca_14-2005.pdf)

After submission of the CTA to the MHRA, the sponsor will receive an acknowledgement letter. If the CTA is judged as valid (i.e., all required information has been provided), the thirty-day assessment period begins. If the CTA is not valid, the sponsor will be informed of the deficiencies and be given an opportunity to update the file. If the deficiencies are major, the sponsor may be requested to withdraw the file and resubmit once it is complete.

Phase I studies involving healthy volunteers have a fourteen-day assessment period.

### Possible outcomes

There are three potential outcomes after the review of the CTA:

1. Acceptance of the request for a clinical trial authorization.
2. Acceptance of the request for a clinical trial authorization subject to conditions.
3. Grounds for non-acceptance (GNA) of the request for a clinical trial authorization.

### Grounds for Non-Acceptance letters

The *Grounds for Non-Acceptance* (GNA) letter will identify the deficiencies or inadequacies in the submission. A sponsor has the opportunity to make an amended request for a CTA by addressing all the issues identified in the GNA letter. No additional changes are permitted. The possible outcomes from the sponsor's amendment are similar to the three original potential outcomes:

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

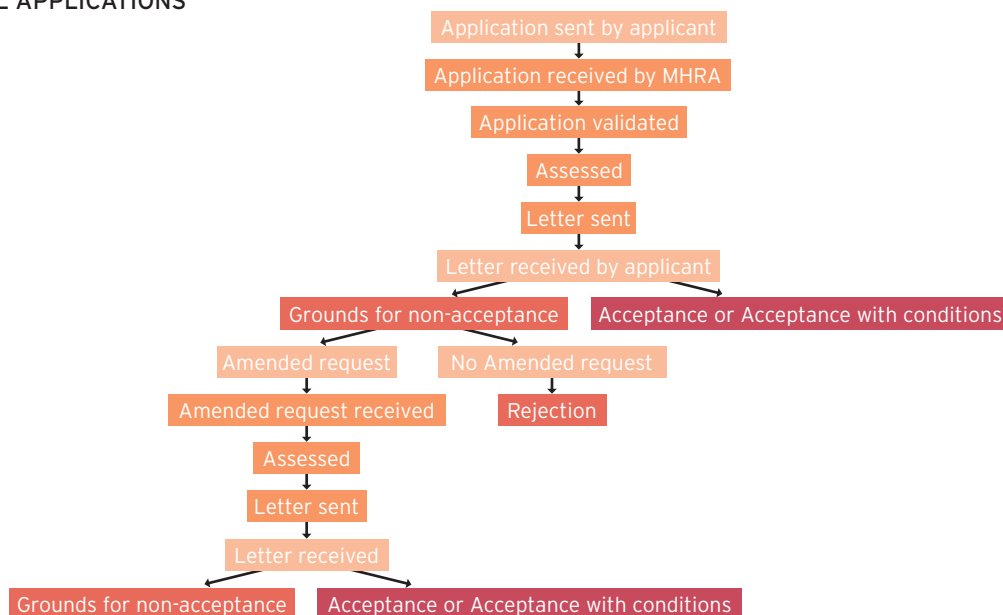
The MHRA targets 60 days from the date of the original application to provide a response on the amendment to the sponsor. Phase I studies involving healthy adults will be assessed within 14 days.

If a sponsor opts not to respond to a GNA letter, the application will be deemed to have been refused as of 60 days from the date of receipt of the original application. In this case, the MHRA does not send a notification letter.

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## Exhibit 1: Clinical trial application process

### INITIAL APPLICATIONS



Source: Medicines and Healthcare products Regulatory Agency,  
<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/>

A clinical trial is not permitted to start until each site has received a favourable opinion from its Ethics Committee.

### Amendments to a trial

The guidance document published by the European Commission<sup>2</sup> also provides details on what types of amendments need to be submitted to regulators.

Non-substantial amendments do not have to be submitted to regulators. However, the changes should be recorded and available on request. In addition, they should be included in the next update to the Investigator's Brochure, if appropriate.

Substantial amendments are those considered likely to have a significant impact on the:

- safety or physical or mental integrity of the subjects
- scientific value of the trial
- conduct or management of the trial
- quality or safety of any investigational product used in the trial

Substantial amendments are required to be submitted to each site's Ethics Committee and the country-specific regulator. An amendment may be implemented once approval has been obtained from the Ethics Committee and the amendment has been submitted to the regulator and there are no grounds for non-acceptance.

### Safety reporting

Similar to the requirements in the US and Canada, sponsors are required to submit safety information on unexpected drug-related serious adverse events to regulators in an expedited manner.

The MHRA must be notified of fatal or life-threatening suspected (meaning, drug-related) unexpected serious adverse events (SUSAR) in an expedited fashion and no later than seven calendar days after information on the SUSAR is received. The sponsor then has a further eight days to submit additional relevant information.

For non-fatal or non-life-threatening suspected unexpected serious adverse events, the report must be submitted within 15 calendar days after the information is received.

### Declaration of end of trial

The end of a clinical trial is considered to take place when the last patient has the last visit. Exceptions to this definition should be justified in the protocol. The sponsor is required to notify the regulator once a trial has ended in the UK (or the given country) as well as in all other countries (if the trial is multinational in scope).

If a trial ends prematurely, the sponsor must notify the regulator within 15 days of when the trial is halted and explain the reasons for terminating the study. If a trial is temporarily halted, the sponsor must also notify regulators within 15 days. Restarting a halted trial requires submitting an amendment as it is considered to be a substantial amendment. If a sponsor elects not to restart a temporarily halted trial, it has 15 days to notify the regulator.

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