HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Clinical Trial Applications

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

CONTENTS

ABBREVIATIONS

CESP	Common European Submission Portal
CHMP	Committee for Medicinal Products for Human Use
CTFG	Clinical Trial Facilitation Group
DSUR	Development safety update report
EDI	Electronic data interchange
EEA	European Economic Area (EU and Norway, Iceland and Liechtenstein)
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EU	European Union
EVCTM	Clinical trials module of the EudraVigilance database
GCP	Good clinical practice
GMP	Good manufacturing practice
HMA	Heads of Medicines Agencies
HPRA	Health Products Regulatory Authority
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual case safety report
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
MPR	Medicinal product report
NIMP	Non-investigational medicinal product dossier
PT	Preferred term
RSI	Reference safety information
SAE	Serious adverse event
SAR	Serious adverse reaction
SI	Statutory Instrument
SmPC	Summary of product characteristics
SUSARs	Suspected unexpected serious adverse reactions
VHP	Voluntary Harmonisation Procedure
XML	Extensible Markup Language (a text-based format to share data)

1 SCOPE

This guide covers applications for clinical trials as defined in the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, SI No 190 of 2004.

Clinical trials which are outside the scope of the Regulations and, therefore, of this guide include:

- Non-interventional trials which are not subject to legislative control when they meet the definition in Regulation 4 of the Regulations.
- Clinical trials involving only medical devices, food supplements, or other non-medicinal therapies (such as surgical interventions). For medical devices, please see the guideline on clinical investigations on the HPRA website.

2 INTRODUCTION

This document is intended to give guidance to applicants in making applications for clinical trials on medicinal products for human use to the Health Products Regulatory Authority (HPRA) as competent authority for these Regulations. Guidance on applications to ethics committees is available on the website of the Department of Health. Information on clinical trials using medicinal products containing genetically-modified organisms is available from the Environmental Protection Agency (see 'GMO Part B Deliberate Release'). (Note that all websites referenced in this document are listed in Appendix 2.)

Clinical trials in Ireland are governed by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, SI No 190 of 2004 and amendments. The Regulations transposed into Irish law the provision of Council Directive 2001/20/EC 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. The Control of Clinical Trials Acts 1987 – 1990 for clinical trials using medicinal products are superseded by these Regulations.

The definition of a clinical trial in the Regulations covers studies on clinical, pharmacological, pharmacodynamic or pharmacokinetic effects or studies to identify adverse reactions to investigational medicinal products, i.e. Phase I to Phase IV studies. Further guidance on the definition of a clinical trial is available in Eudralex, Volume 10, 'Guidance Documents Applying to Clinical Trials, Questions and Answers' available on the website of the European Commission. In particular, the decision tree provided in answer to question 1.1 in the guidance is useful.

Investigational medicinal products include placebo products and both authorised and unauthorised medicines with any type of active substance, including herbal and homeopathic products. Authorised products may be used in accordance with the terms of the marketing authorisation or used in a different way, e.g. at a higher dose, for a new indication or when packaged in a different container.

For additional guidance on making an application for clinical trials and on adverse reaction reporting, applicants should also consult the EU guidelines which are available from the EudraCT website or the website of the European Commission.

Applicants should note that the assessment of a clinical trial application and the assessment of any subsequent application for marketing authorisation for the same medicinal product are two separate assessments. The approval of a clinical trial does not determine the acceptability or otherwise of the marketing authorisation application.

3 REQUIREMENT FOR AUTHORISATION BY THE HPRA

According to Regulation 10 of the Regulations, a trial may only be started or conducted in Ireland if:

- the ethics committee has issued a favourable opinion;
- the HPRA has granted an authorisation;
- the sponsor, or legal representative of the sponsor, is established within the European Economic Area.

4 APPLICATIONS FOR CLINICAL TRIAL AUTHORISATION

Applications for clinical trial authorisation should be made by the trial sponsor or a legal representative acting on behalf of the sponsor. Applications should comply with the European Commission's guideline, '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)' in Chapter 1 of Volume 10 of EudraLex.

4.1 The application

Before an application can be submitted to the HPRA, sponsors must obtain a EudraCT number by logging onto the EudraCT website and following the instructions to obtain a security code and to apply for the EudraCT number. This number, and the email confirmation of the number, must be included with the application. Applications that do not comply with these requirements will not be validated.

The sponsor should then use this unique EudraCT number to create a EudraCT application form and should ensure that the data provided in the EudraCT application form and the XML file are identical and consistent with the protocol.

The submission of the form for 'Additional National Requirements for a Clinical Trial Authorisation' is no longer obligatory. In its place, the HPRA has developed a list of documents

for submission (see Appendix 3) which can be used to facilitate preparation of a new clinical trial application.

The application and all documents must be in the English language.

Applications to the HPRA are made by the sponsor or, if they are not established in the EEA, their legal representative who is established in the Community, or an applicant authorised by the sponsor to make the application.

4.2 Sponsors and investigators

Sponsors

As defined in Regulation 4 the 'sponsor' is the person who takes responsibility for the initiation, management and/or financing of a clinical trial. The sponsor does not need to be located in an EU Member State but must have a legal representative in the EEA. The investigator and the sponsor may be the same person.

The sponsor may delegate any or all of his trial-related duties and functions to another person/organisation. Any duties or functions that are delegated to a third party must be documented and specified in writing in the application form. The sponsor remains ultimately responsible for ensuring that the conduct of the trial and the data generated complies with relevant Council Directives including 2001/20/EC, 2005/28/EC, 2001/83/EC and the Irish Regulations.

For non-commercial multi-centre clinical trials, it is possible to have a local sponsor in addition to an international sponsor. See Section 4.3 for further information relevant to non-commercial (academic) sponsors.

Investigators

The relevant ethics committee is responsible for determining the suitability of an investigator and the quality of the facilities at the clinical trial site.

4.3 Advice for non-commercial (academic) sponsors

Undertaking the role of sponsor of a clinical trial for the first time can be challenging for those in academia and non-commercial organisations. Deciding to assume the responsibility of the role is a significant decision as it entails many legal obligations, for example, safety reporting. Prior to taking that decision, the investigator or organisation needs to consider the resources and infrastructure necessary, and ensure systems and procedures are established that enable the role of sponsor to be fulfilled in a compliant manner.

Sponsors should ensure that they comply with all aspects of legislation and guidance. Information on relevant legislation is referenced in this guide. Some of the key guidance documents are listed here:

- Volume 10 of the publication: 'The rules governing medicinal products in the European Union' contains guidance documents that apply to clinical trials covering application for authorisation, safety reporting, quality, inspections and legislation. This document is available on the EU EudraLex website.
- The ICH guidelines comprise quality, safety, efficacy and multidisciplinary guidelines covering a range of topics, and are available on the ICH website. A key guidance document is the guideline for good clinical practice (GCP): ICH E6 (R2), Good Clinical Practice Guideline (EMA/CHMP/ICH/135/1995; E6 (R2)).

New sponsors are advised to seek expert guidance, to ensure systems and procedures are implemented prior to the start of the clinical trial.

These are just some of the considerations relevant to non-commercial sponsors. For information on non-commercial sponsor system inspections, see Section 12.2.
A 'Clinical Trial Protocol Template' is available to non-commercial sponsors on request to clinicaltrials@hpra.ie.

4.4 Investigational medicinal product dossier and investigator's brochure

Quality, non-clinical and clinical supporting data on the investigational medicinal product (IMP) should be provided in the investigational medicinal product dossier (IMPD) and the investigator's brochure. For further information, please refer to the EU 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials' in Chapter III of Volume 10 of EudraLex. Note that IMPs include not only the test product but also comparators, blinded comparators, blinded test products and placebos.

The investigator's brochure shall be presented in a concise, simple, objective, balanced and non-promotional form that permits an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. Where the IMP already has a marketing authorisation, the summary of product characteristics (SmPC) may be used instead of the investigator's brochure (simplified dossier).

The investigator's brochure must contain reference safety information (RSI), to be used for assessing the 'expectedness' of serious adverse reactions (SARs) that occur during a clinical trial. The RSI is a list of expected serious adverse reactions, which are classified using preferred terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA). An expectedness assessment using the approved RSI should be performed for all serious adverse reactions that occur on a clinical trial. The cover letter submitted with the application should clearly indicate the location of the RSI within the investigator's brochure.

For authorised products, Section 4.8 'Undesirable Effects', of the SmPC includes details of the expected adverse reactions. This document may be used in place of the RSI section of the investigator's brochure. Please note that relevant safety information may also be contained in other sections of the SmPC; however, only Section 4.8 should be used for the purpose of expectedness assessment. If the investigational medicinal product has marketing authorisations in several Member States with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC for the RSI, with reference to subject safety.
If the RSI is within the SmPC, the date of the SmPC used should be specified.

If the reference safety information is included in the investigator's brochure, it should be in a clearly identified separate section. This section should include a list of expected serious adverse reactions clearly arranged according to their nature and frequency (e.g. in tabular format). If different indications are being investigated for the IMP, separate tables of expected adverse reactions by indication may be appropriate to avoid misinterpretation of information, e.g. oncologic indications and immune-mediated indications. Further details on the requirements for RSI can be found in the Clinical Trial Facilitation Group (CTFG) RSI Q&A document on the Heads of Medicines Agency (HMA) website.

If any product used in the trial is a genetically-modified organism, a separate application for a licence must be made to the Environmental Protection Agency. For further details, please contact the agency. A copy of the licence from the agency should be provided with the clinical trial application.

Medicinal products used in the context of a clinical trial, and not falling within the definition of an IMP, are 'non-investigational medicinal products' (NIMPs). The borderline between IMPs and NIMPs and the requirements for NIMPs are described in the EU 'Guidance on Investigational Medicinal Products (IMPs) and Other Medicinal Products used in Clinical Trials'.

If any product used in the trial requires a medical device for its administration or utilisation refer to EudraLex, Volume 10, Guidance Documents Applying to Clinical Trials, Questions and Answers'.

Where a medicine and a medical device are both under investigation, the study is required to comply with the clinical trials legislation for the IMP and the medical devices legislation for the device. A single application to the HPRA can be made which should include the documents referred to in Appendix 3 pertaining to the IMP and the documents required for the clinical investigation of a medical device. The application process will follow the timelines set out in clinical trials legislation and no clock-stops are permitted. A single approval decision will be issued for the study.

4.5 Labelling of the investigational medicinal product

The labels of the immediate and outer container should comply with the requirements of Annex 13 to the EU Guide to Good Manufacturing Practices on 'Manufacture of Investigational Medicinal Products' in Chapter III of Volume 10 of EudraLex. Label text must be in English. Other languages may be included, though, as far as possible, the text for each language should be placed together on the label, rather than placing all language versions of each statement together.

In relation to any changes to the expiry date on the label, the HPRA requires that an additional label be fixed to the outer carton, with the new expiry date, the same original batch number and an explanatory statement highlighting the fact that the expiry date shown on the over-label is a new, approved date, and that the earlier expiry date on the outer and immediate packaging has been superseded. This over-label should not cover either the old use-by date or the original batch number. Any extension to the shelf-life is subject to the submission of an amendment, unless otherwise agreed at the time of the original clinical trial application.

4.6 Subject information and the informed consent procedure

The subject information leaflet and informed consent form, and other information given to the patient in the course of the trial, should not be submitted to the HPRA for information. The relevant ethics committee is responsible for providing an opinion on these documents.

4.7 Ethics committee opinion

In order for a clinical trial record to be released into the EU Clinical Trials Register, the decision taken by the competent authority on completion of the initial assessment (authorised / refused / withdrawn), the opinion of the ethics committee (favourable / not-favourable / withdrawn) and their respective dates must be logged on the EudraCT database by the HPRA. The applicant must provide details of the ethics committee opinion to the HPRA as soon as it is available to ensure that all Irish records are released and published on the EU Clinical Trials Register.

4.8 Procedures for processing of the application

The procedures for authorisation of clinical trials depend on the type of investigational medicinal product in the study. There are two categories of trials:

- General, biological and biotechnological medicinal products
- Advanced therapy medicinal products (gene therapy, somatic cell therapy, tissue engineered products as defined in Article 2 of Regulation (EC) No 1394/2007), or products containing genetically modified organisms

General, biological and biotechnological medicinal products

On receipt, applications are validated in order to check that all the required documentation is present. If documents are missing, the applicant is asked to supply them, and the application is not progressed further until they are provided.

Once validated, the application is assessed and, within 25 days of receipt of a valid application, written notice is sent to the applicant setting out either acceptance of the application for authorisation, with conditions if necessary, or grounds for non-acceptance of the application. If grounds for non-acceptance are sent, the applicant must respond with an amended application (i.e. a response to grounds for non-acceptance) within 14 days. Following assessment of the response and within 60 days of the original application, written notice is sent to the applicant setting out either acceptance of the application for authorisation, with conditions if necessary, or grounds for non-acceptance of the application.

Applicants should note that the Regulations allow for only one cycle of correspondence on any queries which arise from the assessment. If a response is not submitted or the response is not acceptable, the application is treated as rejected (alternatively the sponsor may withdraw the application before day 60). Applicants may contact the HPRA, if necessary, to discuss their responses before submitting them, in order to clarify the changes which are required.

Advanced therapy medicinal products and medicinal products containing genetically modified organisms

For advanced therapy medicinal product clinical trials and trials using genetically modified organisms, the HPRA strongly recommends that the applicant requests a pre-submission meeting to discuss the potential clinical trial submission. The HPRA may consult with its experts before issuing the written authorisation for these trials.

The timelines for this procedure are as follows:
On receipt, applications are validated in order to check that all the required documentation is present. If documents are missing, the applicant is asked to supply them, and the application is not progressed further until they are provided.

Once validated, the application is assessed and within 30 days of receipt of a valid application, written notice is sent to the applicant setting out either acceptance of the application for authorisation, with conditions if necessary, or grounds for non-acceptance of the request. If grounds for non-acceptance are sent, the applicant should respond with an amended application (i.e. a response to grounds for non-acceptance) within 30 days (or longer if the HPRA agrees). The response is assessed by the assessors and by the Clinical Trials Subcommittee. Within 90 days of the original application, written authorisation is sent to the applicant setting out either acceptance of the application for authorisation, with conditions if necessary, or grounds for non-acceptance of the application. Note: This timeframe may be extended in certain

instances by an additional 90 days as per Article 16.2 of the Regulations. The applicant will be notified in writing if the timeline is to be extended.

Applications involving products for xenogenic cell therapy are not subject to any timelines, as provided for in Regulation 16(9) of the Regulations.

Authorisations with conditions

The legislation permits authorisation of a clinical trial with conditions. The conditions are agreed with the sponsor in advance of Day 60/90 and are included in the Day 60/90 approval letter. The approval date is the date of the Day 60/90 letter. When the sponsor has made a submission which addresses the conditions outlined in the approval letter, the HPRA will respond indicating that the conditions have been satisfied. When the condition requires the approval of a substantial amendment to the trial, the HPRA will issue an approval for the amendment; however, the date of approval of the clinical trial remains the date of the Day 60/90 letter.

All application types

The EudraCT database, accessible to all competent authorities of Member States, is updated with the outcome of the process.

4.9 Voluntary Harmonisation Procedure for the assessment of multinational clinical trial applications

The Voluntary Harmonisation Procedure (VHP) is a procedure which makes it possible to obtain a coordinated assessment of an application for a clinical trial that is to take place in several European countries. It consists of the submission of a common dossier to the VHP Coordinator and a coordinated assessment performed by the national competent authorities concerned. After the VHP, a national clinical trial application needs to be submitted by the sponsor according to the national laws for the approval of clinical trials. In the case of a positive outcome from the VHP, the national approval procedure should not take longer than 10 days after the submission of a valid application.

For detailed information on the process and requirements please refer to the 'Guidance Document for a Voluntary Harmonisation Procedure (VHP) for the Assessment of Multinational Clinical Trial Applications' on the HMA website.

4.10 Pharmacogenetic Research

Pharmacogenetic research investigates how genetic variation affects the clinical response to a drug, with the assumption that such knowledge could enhance the efficacy, while reducing toxicity. Clinical trials where samples for pharmacogenetic research are to be collected must comply with GCP. The subject information leaflet and informed consent form must be submitted to the relevant ethics committee for opinion. Pharmacogenetic research must comply with data

protection requirements. Further information on pharmacogenetic research is available on the EMA and ICH websites.

5 AMENDMENTS AND URGENT SAFETY MEASURES

5.1 Amendments by the HPRA

The HPRA may require amendments to be made to the conduct of the trial to ensure compliance with GCP or to ensure the safety or scientific validity of the trials. Where an amendment is required, the HPRA will serve notice on the sponsor that a specified amendment is required in 14 days, and will give the reason for the proposal.

The sponsor may make written representations to the HPRA within the 14 days, which will be taken into account in the final decision. In order to consider the sponsor's response, the HPRA may delay the date on which the proposed amendment is to take effect.

5.2 Amendments by the sponsor

Substantial amendments

Amendments to a trial are regarded as 'substantial' where they are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants, or the scientific value of the trial. It is up to the sponsor to assess whether an amendment is to be regarded as substantial. Substantial amendments to the clinical trial authorisation or accompanying documentation must be notified to the HPRA using the EU 'Substantial Amendment Notification Form'. Further information on substantial amendments is provided in the EU '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)'.

With regard to changes in the quality aspects of the IMPD, guidance is contained in the EMA 'Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials' and the EMA 'Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials'.

A change to the RSI is considered a substantial amendment and should be justified with supporting data. For example, the addition of new expected SAR PTs as well as the update of the frequency of expected fatal and/or life-threatening SARs should always be considered to be substantial. However, changes to the format of the table that do not affect the expected SARs or modifications in exposure rates to expected SARs that do not result in a change in the category of frequency are not considered substantial. Amendments to the RSI should be clearly indicated using track change formatting and mentioned in the cover letter. If the RSI section of an

investigator's brochure is used, it is recommended that amendments to the RSI are made in alignment with the development safety update report (DSUR). In this way, the DSUR can act in part as justification for the RSI changes, and the basis for expectedness can remain consistent for the reporting period. If the RSI is updated prior to the end of the reporting period of the DSUR, detailed justification with supporting data is required.

Non-commercial sponsors using an SmPC are not expected to align the RSI update with the DSUR.

Non-substantial amendments

Non-substantial amendments do not have to be notified to the HPRA; however, they must be recorded and submitted with a subsequent substantial amendment notification. This is particularly important for the clinical trial application form which should be updated in its entirety on the occasion of a substantial amendment. The updated form (XML file) should be submitted to the HPRA so that the EudraCT database can be updated. Non-substantial amendments can be listed on the cover letter accompanying a substantial amendment. There is no requirement to provide any documentation for the non-substantial changes.

Changes to the trial site or investigator

Substantial amendments relating to the clinical trial site or the investigator, which are required to be sent to the ethics committee, should be notified to the HPRA following approval by the ethics committee. A revised XML file with an updated list of approved trial sites/investigators (Section G) should be submitted as part of the next substantial amendment application for the trial.

Updates to the investigator's brochure

In accordance with the legislation, the investigator's brochure is required to be validated and updated at least once a year. Revisions should be clearly indicated and justified. In particular, any change in the 'expectedness' of an adverse drug reaction, including any increase in the specificity or severity of a previously expected reaction should be addressed in the RSI. For ongoing trials, if the RSI is not in a clearly identified separate section with the list of expected adverse reactions clearly arranged according to their nature, frequency and severity (e.g. in tabular format), this should be implemented at the next update.

Revisions to the investigator's brochure can be substantial or non-substantial. The sponsor should verify which revisions are substantial and submit these as substantial amendments.

If a decision cannot be made regarding the classification of an update as substantial or non-substantial, the sponsor is advised to submit the revised investigator's brochure as a substantial amendment to the HPRA. In addition, comment should be provided on the impact of any

updates on the study and consequential substantial amendments to the protocol and/or patient information leaflet should be submitted, where necessary.

Documentation

Amendment applications consist of:
- Covering letter, including the EudraCT number, the CT number assigned by the HPRA, the protocol number(s) affected by the amendment and the trial title
- EU 'Substantial Amendment Notification Form'
- Relevant extracts from the documents that are changed, highlighting current and proposed wording, where applicable
- New version of documents (including the clinical trial application form) if changes are made
- Supporting data

A substantial amendment application may cover an amended document in more than one clinical trial application which uses the same active substance, or it may cover a number of amendments to different documents in the same clinical trial application. Where the amendment relates to a number of clinical trial applications, the EudraCT numbers, CT numbers, and protocol numbers must be clearly indicated in the cover letter.

Amendments to information that is assessed by both the HPRA and the ethics committee should be submitted in parallel to both organisations.
Documentation on non-substantial and substantial amendments should be available, on request, for inspection at the trial site and/or the sponsor's premises, as appropriate.

Procedure for substantial amendments

Once validated, the application is assessed and, within 35 days of receipt of a valid application, written notice is sent to the applicant setting out either acceptance of the application, with conditions if necessary, or grounds for non-acceptance. If grounds for non-acceptance are sent, the applicant must respond with an amended application (i.e. a response to grounds for non-acceptance) not later than 30 days after receiving the grounds for non-acceptance and at least 14 days before the amendment is due to be made. Following assessment of the response and within 14 days of receipt of the response, written notice is sent to the applicant setting out either acceptance of the application for amendment of the authorisation, with conditions if necessary, or grounds for non-acceptance.

5.3 Urgent safety measures

If the sponsor and investigator(s) consider that urgent safety measures need to be taken to protect the health or safety of trial subjects, the sponsor should notify the HPRA in writing no later than three days after the date the measures were taken. The notification should specify the measures taken, the reasons for them and the plan for further action and should be sent to clinicaltrials@hpra.ie. Urgent safety measures notified by telephone must also be notified in

writing no later than three days after the date the measures were taken. An application for amendment, detailing the changes to the clinical trial documents, should be submitted to the HPRA as soon as possible after the implementation of urgent safety measures.

A temporary halt to a trial can be a substantial amendment or part of an urgent safety measure. The restart of the trial should be treated as a substantial amendment with evidence provided that it is safe to restart the trial.

6 END OF TRIAL DECLARATIONS

The end of a trial, whether it ends earlier than planned or according to the protocol, must be notified to the HPRA using the EU Declaration of the End of Trial form. If a trial ends in Ireland before it has ended globally, the sponsor should complete this form to notify the HPRA of the local or national end of trial. This notification can be used as justification for no longer submitting amendments or DSURs. This local end of trial date is also published in the EU Clinical Trials Register. The EU Declaration of the End of Trial form should also be submitted when the trial has ended in all countries in which it was taking place (global end of trial). If the national and global end dates coincide, the form should be submitted only once.

When the trial is terminated prematurely, the end of clinical trial declaration should also provide the following information:
- Justification for the premature ending of the trial
- Number of patients still receiving treatment at time of study termination
- Proposed management of patients receiving treatment at time of study termination
- Consequences for the evaluation of results

The form should be received within 90 days of the end of the trial or within 15 days if it has ended earlier than planned.

7 NOTIFICATION OF ADVERSE REACTIONS/EVENTS

7.1 Reporting suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) occurring during clinical trials undertaken in Ireland should be notified electronically and in parallel to both the HPRA and the clinical trials module of the EudraVigilance database (EVCTM) by investigators or sponsors, in accordance with the 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, CT-3' and the requirements specified in the HPRA 'Guide to Electronic Submission of ICSRs and SUSARs Associated with the Use of Human Medicines'.

Paper reporting should be exceptional and in line with the 'Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MRPs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area.'

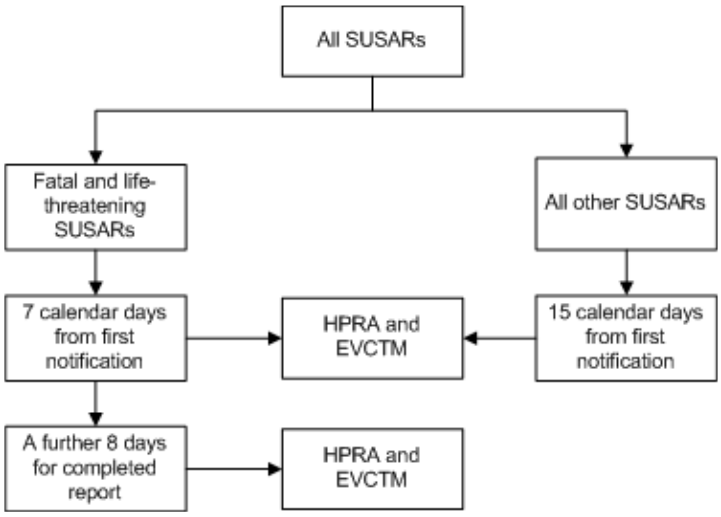
Whichever form/format is used, it is important that the basic information/data elements described in Annex 3 of the above detailed guidance are included, when available, in any expedited report.

In exceptional cases, the HPRA will assist academic sponsors with electronic report submission to EVCTM if necessary. In such cases, a request should be submitted to medsafety@hpra.ie at the time of submission of the CT application, to facilitate timely completion of arrangements.

The timelines for expedited reporting are shown in the figure below. The timelines start as soon as the sponsor has first knowledge of the minimum criteria required for expedited reporting. The timelines also re-start if/when additional case information becomes available. Please note that in situations where the HPRA is assisting academic sponsors with electronic report submission to EVCTM, the timelines for submission will be shortened to facilitate HPRA processing of cases prior to submission. This will be considered in the context of requests to the HPRA to undertake such reporting, with timelines for submission agreed on a case by case basis as part of the agreed arrangements.

Other safety issues requiring expedited reporting should be notified in accordance with the criteria defined in the above detailed guidance document.

As a general rule, treatment codes should be broken/unblinded by the sponsor before reporting a SUSAR. However, in certain circumstances (e.g. trials in high morbidity or high mortality conditions where efficacy endpoints could also meet the criteria for reporting as SUSARs) and where it is considered that the integrity of the trial may be compromised if the blind is systematically broken, sponsors should seek **prior** approval from the HPRA regarding proposed arrangements for reporting of SUSARs. In such cases, an independent Drug Safety Monitoring Board is recommended.



7.2 Monitoring and reporting of adverse events

The sponsor is required to keep detailed records of all adverse events relating to a clinical trial which are reported to him or her by the investigator(s) for that trial. The HPRA is entitled to request these records.

7.3 Line listings

A list of the suspected serious adverse reactions to an IMP that have occurred in clinical trials during the Development Safety Update Report (DSUR) reporting period is required as per SI 190/2004. Examples of the details to be included and format of the line listings are available on the ICH website. Copies of line listings are not routinely required by the HPRA. However, it should be noted that copies of these line listings may be requested and, as such, should be made available to the HPRA when required.

7.4 Development Safety Update Reports

In addition to the expedited reporting requirements of individual SUSARs, sponsors are required to submit once a year, or on request, a safety report to the HPRA. Since September 2011, the DSUR has replaced the EU Annual Safety Update Report and differs from it in a number of ways. For example, there is a common birth date, the Development International Birth Date (DIBD). The report includes information on the marketing authorisation status worldwide, the cumulative exposure in clinical trials and marketing experience (if applicable), and a summary of the important risks.

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

1 examining whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational medicinal product's safety;
2 describing new safety issues that could have an impact on the protection of clinical trial subjects;
3 summarising the current understanding and management of identified and potential risks; and
4 providing an update on the status of the clinical investigation/development programme and study results.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

Guidance on the preparation on the report is provided in the ICH Guideline E2F in Chapter II of Volume 10 of EudraLex.

A DSUR should not be submitted as a substantial amendment; however, the sponsor is required to verify whether the data presented in the report necessitate an amendment to the documentation submitted with the request for authorisation of the clinical trial. If this amendment is substantial, the rules for notification of substantial amendments apply to these changes.

A DSUR is required to be submitted annually to the HPRA, with the following exceptions:
a) Trials that have not started recruitment in Ireland.
b) Trials that are in follow-up in Ireland (subjects not receiving IMP).
c) Trials that have ended in Ireland as defined by the sponsor in the clinical trial application form (Section E.8.8).

A safety evaluation, including data from the entire duration of the trial, should be included in the End of Trial Report (see Section 10). For a) and b) above, notification as to why the DSUR is not being submitted should be provided to clinicaltrials@hpra.ie.

8 SUSPENSION OR REVOCATION OF A TRIAL

The HPRA may issue a notice to suspend or end the trial or to end it at one or more trial sites if it considers that:
- the conditions of the approval or of application itself are not complied with, or
- there are doubts over the safety or scientific validity of the study, or
- there are doubts over the conduct of the trial at a particular site.

The notice will be sent to the sponsor, or the investigator at each site or particular sites, as appropriate. It will specify the actions to be taken, the duration of the actions and the conditions which must be satisfied before the trial may recommence. The relevant ethics committee, other Member States, the EMA and the European Commission will also be informed.

The notice will be sent with immediate effect if the HPRA considers that there is an imminent risk to the health or safety of trial subjects. Otherwise, the sponsor or investigator will be notified at least one week in advance and given the opportunity to make representations to the HPRA. Any issued notice remains in force, even if appealed.

The suspension or revocation of a trial in another Member State may impact on the authorisation of similar trials in Ireland.

The EudraCT database is updated following suspension, revocation or early termination, temporary halt or re-start of a clinical trial.

9 APPEALS/ REPRESENTATIONS

A sponsor may appeal by making a representation relating to a decision of the HPRA to the HPRA's Advisory Committee for Human Medicines in the following situations:

- The HPRA has authorised a trial with certain conditions.
- The HPRA has issued grounds for not accepting a request for authorisation or for amendment of the authorisation after the sponsor has amended the request.
- The HPRA has amended a trial authorisation.
- The HPRA has issued a notice for suspension or termination of a trial.

The representation must be sent within 28 days of the HPRA's decision, unless further time is requested and granted. The appeal will be considered by the committee, which will report its findings and advice to the Authority. The HPRA will notify the sponsor of the outcome of its deliberations.

10 CLINICAL TRIAL SUMMARY (END OF TRIAL) REPORT

Since 21 July 2014, it is mandatory for sponsors to post the clinical trial summary or end of trial report containing the clinical trial results to EudraCT. This date corresponds to the finalisation of the programming of the database as referred to in the European Commission guideline (2012/C 302/03), in the application of the Clinical Trials Directive 2001/20/EC and in the Paediatric Regulation. Under these frameworks, as sponsors start to comply with their legal obligation to provide end of trial reports to EudraCT, summary results of clinical trials will become available via the publicly accessible European Union Clinical Trials Register. The European Commission guideline on the posting and publication of result-related information on clinical trials is available on the EMA website.

The requirement for a clinical trial summary report applies to trials that are completed or terminated prematurely. Guidance on the modalities and timing of posting of the report is available on the EudraCT website. The format of the end of trial report should comply with the guidance in Chapter V, Volume 10 of EudraLex.

An end of trial report should not be submitted to the HPRA.

11 ARCHIVING

The sponsor and the investigators are required to retain the essential documents relating to a clinical trial for at least five years after its completion. The essential documents are defined as those that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced, and this is referred to as the trial master file (TMF). These documents should be filed in an organised way that facilitates management of the clinical trial, audit and inspection by competent authorities and should be readily available on request.

The HPRA requires that if an end of trial report has not been submitted (see Section 10 above) then the essential documents should be retained indefinitely.

Sponsors and investigators may be required by other applicable requirements to retain the essential documents for more than five years. Further information is available in the EU guideline on 'Recommendation on the trial documentation and archiving.'

The requirements for marketing authorisation holders to arrange for the retention of essential clinical trial documents by the owners of the data are outlined in Commission Directive 2003/63/EC (in Volume 1 of EudraLex).

12 GCP INSPECTIONS

12.1 Information for inspectees

The HPRA may perform a Good Clinical Practice (GCP) inspection at a clinical trial site. The purpose of a GCP inspection is to verify if the requirements of the Regulations and relevant guidance, including Volume 10 of the publication 'The Rules Governing Medicinal Products in the European Union', have been met.

Inspections are performed according to the procedures described in Chapter IV – Inspections of Volume 10 of the publication 'The rules governing medicinal products in the European Union'.

In accordance with Article 15(1) of Directive 2001/20/EC, any site involved in a clinical trial may be subject to inspection, such as the investigator sites, any laboratory used for clinical trial

analyses and the sponsor's premises. Contract research organisations/facilities, acting under arrangements with a sponsor or investigator to perform some or all of the functions of the sponsor or investigator, may also be subject to GCP inspection.

Inspections may be conducted on a routine basis, or may arise as a result of a specific trigger. Inspections may be conducted on ongoing or completed studies and may be announced or unannounced; however, they are generally announced. Typically, inspectees will be given approximately one month's notice of a forthcoming inspection.

The following information may be requested from the inspectee prior to the inspection:
- Patient status per trial site (number randomised, drop-out rate, number of serious adverse reactions reported per site).
- Copies of company standard operating procedures, e.g. monitoring procedure, informed consent procedure, serious adverse event reporting procedure, drug supply management procedure.
- Trial-specific documents such as a copy of the current protocol and informed consent form, source data verification guidelines, product handling instructions, laboratory manual, randomisation code breaking procedure, monitoring plans and reports.
- Job descriptions and CVs of key site and sponsor personnel.
- Any other documentation deemed necessary by the inspectors.

An inspection plan, outlining the units to be inspected, the time and duration for each major inspection activity and the schedule of meetings to be held with the investigator and/or sponsor personnel, will be provided to the inspectee prior to the inspection.

In accordance with the Regulations, the trial master file, comprising the essential documents which enable both the conduct of the trial and the quality of the data produced to be evaluated, must be available by direct access and form the basis for the GCP inspection.

The conduct of a GCP inspection can vary depending on its scope. Following an inspection, a report is issued to the inspectee, and a response to any findings is required to be submitted. Once all findings and observations of the inspection have been addressed satisfactorily, the inspectee will be advised that the inspection is closed.

12.2 Advice for non-commercial (academic) sponsors regarding GCP inspections

While the same inspection procedures and reference documents are used to determine compliance of all sponsors, irrespective of commercial status, the HPRA recognises that Chapter IV – Inspections of Volume 10 of the publication 'The Rules Governing Medicinal Products in the European Union', primarily concerns inspections of clinical trials performed in connection with prospective marketing authorisation applications. Therefore, in order to assist non-commercial sponsors with inspection readiness, a description of the key systems that are typically examined during GCP inspection of a non-commercial sponsor are outlined below:

- **Organisation and personnel**: Inspectors examine how the sponsor has distributed duties and tasks for the trial, and that roles and responsibilities are clearly defined, including in written agreements with third parties, where applicable. In the non-commercial setting, it is typically seen that the role of medical expert may be assigned to a principal investigator or a safety committee (as appropriate) and/or other duties and tasks may be transferred or shared with other non-commercial entities as part of cooperative groups. All such arrangements are reviewed on inspection, including, but not limited to, verifying that the sponsor has considered the trial organisation as part of its quality risk management (ICH E6 (R2), Section 5), that a clear and timely record of roles and responsibilities was made, that the sponsor has qualified that the party undertaking a task can do so in a compliant manner, and that mechanisms are in place to maintain oversight.
- **Facilities and equipment**: Inspectors review the adequacy of facilities required for sponsor activities, such as trial master file storage and archive. The validation status of any electronic equipment/computerised systems will also be confirmed. Non-commercial sponsors should ensure that electronic equipment/computerised systems, used to fulfil a trial purpose, have been validated taking into consideration the requirements of GCP.
- **Quality risk management**: The quality system is examined in detail, including compliance with ICH E6 (R2), Section 5. Activities including, but not limited to, the following are reviewed: quality risk management processes, document control, training, change control, compliance monitoring (e.g. deviations, auditing). The HPRA wishes to highlight that, when a risk-based approach to a GCP activity is taken, it is important that the sponsor retains a record of the rationale for and approval of that approach, as such documentation may be requested on inspection. Records could range from meeting minutes to completion of more formalised risk assessment tools.
- **Implementation and termination of the trial**: The availability of regulatory and ethics opinions and that of any other statutory body are examined. The inspectee will be asked to demonstrate that it has adequate insurance coverage as a sponsor. Inspectors will also check that the sponsor has procedures to ensure compliance with the regulatory procedures outlined elsewhere in this guide (e.g. Section 5, 6, and 10) and to ensure the completeness and accuracy of documents submitted. For example, a key procedure examined during inspection is the process for preparation of the clinical trial protocol and amendments, including confirmation that input from relevant experts was sought and that quality control was applied to confirm internal consistency as well as consistency with other related documents (e.g. investigator brochure, case report form, patient information leaflet/consent form, monitoring plan).
- **Monitoring:** Monitoring procedures will be reviewed in detail, including plans for on-site monitoring, central monitoring and data committee monitoring, as applicable. The sponsor must be able to demonstrate that it has oversight of trial conduct and GCP compliance and has mechanisms in place to continuously monitor the benefit-risk balance. Documents requested may include risk assessment, monitoring plans, follow-up letters, GCP non-compliance escalations, data committee charters and meeting minutes.
- **Investigational medicinal product:** GCP inspections focus particularly on distribution and shipping of IMPs to the investigator site(s), labelling, and guidance provided to investigators. Where applicable, procedures for unblinding and randomisation will also be reviewed.

- **Safety and adverse event (AEs) reporting:** The pharmacovigilance system will be inspected, including, but not limited to, procedures for collecting and processing AEs/any other events specified in the clinical trial protocol, identifying and reporting SUSARs, managing reference safety information, communicating to the HPRA/ethics committees/investigators and DSUR preparation and submission. It should be noted that assistance from the HPRA to academic sponsors with electronic report submission to EVCTM does not obviate sponsor obligations from other responsibilities under CT-3 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use'.
- **Non-compliance:** Sponsor procedures to deal with significant and/or persistent non-compliance, including processes for performing root cause analysis and implementing corrective and preventative actions, will be examined.
- **Data handling and clinical trial report:** Systems and procedures to collect clinical trial data and to process and report those data are examined, with a focus on data integrity and credibility. Key processes subject to inspection include the quality of the case report form, mechanism for entry of data into the clinical database, quality assurance/quality control of data (QA/QC, also known as 'data cleaning'), audit trails, data locking and analysis/reporting.
- **Documentation archiving:** The sponsor system for maintaining the clinical trial master file (from before, during and after the trial) will be reviewed. The sponsor should also have a person appointed as responsible for trial archive.

The above areas are indicative of the types of areas examined during a GCP inspection of a non-commercial sponsor. However, additional areas may also be covered depending on the nature of the trial and the objectives of the inspection.

13 MANUFACTURING AUTHORISATIONS

Investigational medicinal products (IMPs) used in trials must be manufactured in accordance with the requirements of the 'EU Guidelines on Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use' (volume 4 of the Rules Governing Medicinal Products in the European Union). Each company responsible for manufacture (including assembly or batch certification) must have a manufacturing authorisation which covers the IMP. The authorisation is issued by the competent authority in the Member State (including EEA countries) where the company is situated and it must show that the manufacturer is authorised to manufacture or assemble the relevant pharmaceutical form (e.g. solid dose forms, solutions for injection, etc.). Manufacturing authorisations for all manufacturing, assembly and batch certification sites must be provided as part of an application to conduct a trial.

Where a product is manufactured outside the EU/EEA, the company which imports it into the EU/EEA must hold a manufacturing authorisation for this 'third-country' importation. The qualified person in the importing manufacturing company must satisfy him/herself of the GMP status of the manufacturing site outside the EU/EEA. The HPRA also reserves the right to conduct GMP inspections at such sites. With the exception of comparator products, it is not necessary for batches of investigational medicinal products to be re-tested on importation into

the EU. Where the importer does not have access to the original manufacturer of a comparator product or to the manufacturer's certification of the batch(es) concerned, each such batch of comparator should be tested on importation. In all cases, each imported batch of an investigational medicinal product must be certified before release by the qualified person of the manufacturer responsible for batch release.

The Regulations provide for an exemption from the need for a manufacturing authorisation for certain manufacturing operations carried out in hospitals. No authorisation is needed for labelling, packaging or re-packaging (including re-constitution) of a product by a doctor, pharmacist or other person acting under the supervision of a pharmacist, when the product is for use only in the hospital by a resident patient or an out-patient.

14 ENFORCEMENT

The HPRA is the responsible body for enforcement of the Regulations in Ireland and may prosecute for any offences committed. The HPRA may also issue infringement notices where it has objective grounds for considering that any person has contravened any provision of the Regulations.

APPENDIX 1 FEES AND ADDRESSES FOR THE APPLICATION

The HPRA strongly recommends electronic submission of clinical trial and related information in line with the 'Guide to Electronic Submissions - Human Medicines'.

Address for applications of a new clinical trial
New clinical trial applications should be submitted by CESP or sent on CD/DVD or memory stick to:

Receipts and Validation
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77

Address for applications for clinical trial amendments and development safety update reports
Amendments and development safety update reports should be submitted by CESP or sent to

submissions@hpra.ie

or sent on CD/DVD to:

Receipts and Validation
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77

Address for submission of urgent safety restrictions, end-of-trial declarations, and responses to grounds for non-acceptance letters:

clinicaltrials@hpra.ie

or

Clinical Trials Unit
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77

Address for reporting adverse reactions and SUSARs

medsafety@hpra.ie

or

Pharmacovigilance Section
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77

or

Fax: +353 1 676 2517

Address for manufacturing authorisation applications and amendments

compliance@hpra.ie

or

Compliance Department
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77

Fees for applications

The HPRA 'Guide to Fees for Human Products', the 'Fee Application Form for Human Products' and details on payment are available from the 'Publications and Forms' section of www.hpra.ie. Payment is to be made with the clinical trial application. Fees are payable to the account of the Health Products Regulatory Authority.

Swift Code: AIBKIE2D
IBAN: IE 54 AIBK 931012 33712185
Allied Irish Bank
1-3 Baggot Street Lower
Dublin 2

VHP clinical trial applications as well as substantial amendments of former VHP trials can be submitted to the VHP Coordinator: VHP-CTFG@VHP-CTFG.eu.

APPENDIX 2 WEBSITES REFERENCED IN THIS GUIDELINE

The website of the European Commission, EudraLex Volume 10: Clinical Trials contains:
- Chapter 1 Application and Application Form
- Chapter II Safety Reporting
- Chapter III Quality of the Investigational Medicinal Product
- Chapter IV Inspections
- Chapter V Additional Information (includes Questions and Answers Document referenced in section 2 of this guideline)

Other European legislation relevant to medicinal products is available in Volumes 1 and 4 of EudraLex.

The website of the European Medicines Agency contains scientific guidelines as referenced in this guideline, including the Good Clinical Practice Guideline (EMA/CHMP/ICH/135/1995; E6(R2))

Please see the HPRA website (www.hpra.ie) for the following information on clinical trials:
- Clinical Trial Subcommittee meeting dates and submission cut-off dates, for each year
- 'Terms of Reference and Rules of Procedure of the Clinical Trial Subcommittee'
- 'Guide to Clinical Trial Applications'
- A 'Clinical Trial Protocol Template' is available to non-commercial (academic) sponsors on request to clinicaltrials@hpra.ie
- Information on educational seminars

Please see the Medical Devices section of www.hpra.ie for information on clinical investigations of medical devices.

The website of the Department of Health (www.health.gov.ie) contains:
- European legislation
- National legislation
- Guidance for ethics committees

The website of the HMA contains:
- Information on the Clinical Trials Facilitation Group
- Documents produced by the group, including the guidance document for the voluntary harmonisation procedure referred to in section 4.9 of this guideline
- Recommendations related to contraception and pregnancy testing in clinical trials
- Information on Reference Safety Information

EudraCT is a database of all clinical trials commencing in the Community from 1 May 2004. Information on clinical trials conducted in the EU/EEA is available on the EU Clinical Trials Register.

The website of the ICH contains:

- Quality, safety, efficacy and multidisciplinary guidelines and definitions
- The Guideline for Good Clinical Practice (E6(R2)); this document is also available on the EMA website

The website of the EU Clinical Trials Register contains publicly available information on interventional clinical trials on medicines.

The website of the Environmental Protection Agency in Ireland.

APPENDIX 3 LIST OF DOCUMENTS FOR SUBMISSION

Please see below the list of documents for submission of a new clinical trial application.

(i)	Receipt of confirmation of EudraCT number
(ii)	Cover letter: in accordance with CT-1, the letter should indicate the specific features of the trial population such as trial participants not able to give informed consent or minors and whether the trial involves the first administration of a new active substance to humans
(iii)	Valid EudraCT XML file
(iv)	Clinical trial application form (signed copy)
(v)	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor
(vi)	Protocol (with all current amendments), including summary
(vii)	Investigator's brochure
(viii)	Investigational Medicinal Product Dossier (IMPD) or simplified IMPD
(ix)	Non-investigational medicinal product (NIMP) dossier (if required)
(x)	Copy of the ethics committee opinion, if available
(xi)	Summary of scientific advice from any Member State or the European Medicines Agency (EMA) for this trial
(xii)	Copy of the EMA decision on the Paediatric Investigational Plan (PIP), where relevant
(xiii)	
a)	Copy of manufacturing authorisation(s) if the IMP is manufactured and/or batch released in the EU/EEA
b)	Copy of authorisation to cover trials or products with special characteristics, e.g. GMOs, radiopharmaceuticals
c)	Declaration of the QP that the manufacturing site operates in compliance with GMP at least equivalent to EU GMP, if manufactured outside the EU/EEA
d)	Declaration of GMP status of active biological substances
(xiv)	Examples of labelling
(xv)	HPRA fee form and proof of payment