

Guide to Clinical Trials Conducted under the Clinical Trials Regulation (CTR) in Ireland



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

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ABBREVIATIONS

ACT-EU	Accelerating Clinical Trials in the EU
ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Product
AxMP	Auxiliary Medicinal Product
CHMP	Committee for Medicinal Products for Human Use
CRG	Compliance Regulatory Group
CTAG	Clinical Trials Coordination and Advisory Group
CTCG	Clinical Trial Coordination Group
CTD	Clinical Trial Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
EC	European Commission
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 (the HPRA is a member of the HMA)
HPRA	Health Products Regulatory Authority
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IVDs	In Vitro Diagnostics
MIA	Manufacturer's / Importer's Authorisation
MS(s)	Member State(s)
MSC	Member State Concerned
NREC	National Research Ethics Committee
OMS	Organisation Management Service (EMA)
RFI	Request for Information
RMS	Reporting Member State
saMS	Safety assessing Member State
SI	Statutory Instrument
SUSARs	Suspected Unexpected Serious Adverse Reactions

1 INTRODUCTION

Clinical trials contribute significantly to advances in medical treatment. They may be conducted for a range of purposes, for example to test whether a new treatment or combination of treatments is safe and effective, or to explore new ways to use existing medicines.

The EU Clinical Trials Regulation (Regulation No 536/2014, hereafter 'CTR'), was adopted on 16 April 2014, and became applicable on 31 January 2022.

The CTR was designed to benefit patients and medical research in Europe by streamlining the approval of clinical trials across the Member States with the aim of creating a favourable environment for conducting trials in the EU while also ensuring that the highest standards of safety for participants are maintained.

Key features of the CTR include:

- Single submission and approval of mononational and multinational clinical trial applications through an EU clinical trial portal and database known as the Clinical Trial Information System (CTIS), hosted by the European Medicines Agency (EMA)
- A single fee per Member State
- Identical rules for conducting clinical trials throughout the European Union (EU)
- Strictly defined timelines for assessment
- Increased efficiency of the approval process for clinical trials

The EU and Member States continue to undertake a range of coordinated initiatives aimed at fostering a more supportive and competitive environment for research and development in Europe. These efforts focus on streamlining regulatory processes, enhancing collaboration between regulators and stakeholders, and promoting innovation while maintaining high standards for quality, safety, and efficacy. Key initiatives such as ACT EU (Accelerating Clinical Trials in the EU) are intended to improve the efficiency and attractiveness of the EU clinical trials landscape. For further information, please refer to the ACT EU, EMA, HMA and European Commission websites.

This guide describes the conduct of clinical trials under the CTR in Ireland. **It should be read in conjunction with EU and national legislation, and EC, CTCG and EMA guidelines.** A list of relevant documents is provided in the references section of this guide.

2 CLINICAL TRIALS UNDER THE CTR

2.1 Scope

This guide covers clinical trials as defined in the CTR, that are intended to be conducted, or are being conducted, in Ireland under the CTR.

Clinical trials outside the scope of the CTR and, therefore, not covered by this guide include:

- Non-interventional studies as defined in the CTR.
- Clinical studies involving only medical devices, food supplements, or other non-medicinal therapies (such as surgical interventions). For medical devices, please refer to the HPRA 'Guide to clinical investigations carried out in Ireland', which can be found on the HPRA website at www.hpra.ie.

The Clinical Trials Coordination and Advisory Group (CTAG) have developed a CTR Questions & Answers document; Annex I includes a decision tree that may assist in determining whether a study falls under the scope of the CTR. Please see the HPRA supports section of this guide if further regulatory classification advice is required.

2.2 Clinical Trials Information System (CTIS) and transparency

The Clinical Trials Information System (CTIS) is an EU-wide submission portal and database, hosted by the EMA and designed to support the application of the CTR. Sponsors, Member States (MSs), the European Commission (EC) and the public have access to different aspects of the system comprising of two restricted and secured workspaces and one publicly accessible website and clinical trials map.

CTIS facilitates the harmonisation of both the submission and assessment of clinical trials across the European Union (EU) and acts as the primary submission portal for all applications and for communications between sponsors and MSs.

The CTR has increased the transparency of clinical trial activity in the EU, and the publication of certain trial-related information by sponsors is subject to strict timelines as set out in the CTR. Annex I of the revised CTIS transparency rules and CTIS sponsor handbook (section 2.1 and 2.2) provides further information on CTIS publication rules, types of information and timing of publication depending on the trial category.

The CTIS transparency rules allow stakeholders to access information on trials being conducted in the EU, and on completed trials via the publicly accessible CTIS website and clinical trial map.

In particular, patients can utilise the provided information to make informed decisions regarding participation in a trial or to access the results of a trial in which they were involved. The CTIS public portal can also support healthcare professionals in identifying suitable trials for their patients. Therefore, it is important that sponsors promptly update CTIS with the trial's recruitment status (CTR Article 36), update the structured data fields with proposed changes when submitting modification applications to an authorised trial and upload the summary of results to CTIS within one year of the trial ending in EU (CTR Article 37).

2.3 Applications

A sponsor wishing to conduct a clinical trial in Ireland under the CTR, must submit a single application through CTIS, which consists of Part I (documents relevant for all MSC) and Part II (national documents for each MSC). The application should not be sent directly to the HPRA or the National Office.

The sponsor decides which MSs to include in their application. These are referred to as 'Member States Concerned' (MSCs). Sponsors are encouraged to include all EU/EEA MSs where the clinical trial is planned to be conducted with the initial clinical trial application, however, sponsors also have the option to add further MSCs after authorisation of the clinical trial.

The sponsor should nominate an MSC to be the lead or 'Reporting Member State' (RMS), however, the proposed RMS may not always become the final RMS.

The CTIS Sponsor handbook provides guidance on creating and submitting initial and substantial modification application in CTIS.

Further information on the documents to be included in a clinical trial application for Part I and Part II assessment is provided in Annex I of the CTR. Documents to be submitted with substantial amendments are listed in Annex II of the CTR.

Proof of payment is required to be submitted as part of the application dossier in CTIS. For further information on fees, see section 3.12 of this guide.

Part-1 only initial applications

Sponsors have the option of submitting their application in two phases up to two years apart. Under Article 11 of the CTR, sponsors can submit Part I only initial applications for one or more MSCs. Part II documents for those MSCs can be submitted at a later date within two years of the initial application. Complete Part II documents must be submitted and authorised before a trial can start in each country.

To avoid CTIS issues and allow all MSCs to be included in any future substantial modifications to the trial, sponsors are advised to submit Part II dummy documents for each Part I only MSC. When submitting Part I only initial clinical trial applications in CTIS, please consult the CTCG 'Guidance for sponsors on Article 11 workaround' which can be found on the HMA website.

2.4 Authorisation process

There are two parts to the assessment, prior to a single national decision in each Member State:

- Part I includes assessment of the protocol, investigator's brochure and investigational medicinal product dossier (IMPD). Assessment of these documents, within EU-mandated timelines, is led by the RMS, with MSCs providing comments.
- Part II includes assessment of the subject information and informed consent documents, the suitability of the investigator and of the trial site, indemnity and data protection. This assessment is done at national level by each national ethics committee.

Each MSC will consider the RMS's conclusion on Part I, and the ethics committee's opinion on Part II, and issue their single national decision via CTIS. A trial cannot commence in an MSC until the single national decision has been issued.

2.5 Risk-proportionate approaches and low intervention clinical trials

Risk-proportionate approaches, including the concept of 'low intervention' clinical trials, were introduced in the CTR. Sponsors should indicate in the cover letter of the clinical trial application if they consider a clinical trial to be a low intervention trial and must provide detailed justification thereof.

For more detailed information, refer to 'Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use' document, located in EudraLex Volume 10.

3 IMPLEMENTATION OF THE CTR IN IRELAND

3.1 National legislation

The CTR is directly implemented into Irish legislation, and is directly applicable to all stakeholders referenced in the CTR. However, national legislation is required to deal with matters relevant to an individual Member State.

This Irish legislation comprises:

- European Union (Clinical Trials) Regulations 2022 (S.I. No 99/2022), implementing the CTR, and setting out the responsibilities of each of the stakeholders, and the powers of the HPRA ('the Authority') at national level;
- European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022 (S.I. No 41/2022), establishing the National Office for Research Ethics Committees (hereafter 'National Office') and the National Research Ethics Committees for clinical trials;
- Medicinal Products (Control of Manufacture) (Amendment) Regulations 2022 (S.I. No 43 of 2022), amending the Medicinal Product (Control of Manufacture), Regulations 2007 (S.I. No 539/2007).

The national legislation does not introduce requirements over and above those outlined in the CTR.

3.2 Coordinated review

In Ireland, a coordinated procedure for scientific and ethical assessment of clinical trials has been developed by the HPRA and the National Office for Research Ethics Committees (hereafter 'National Office', [Home - NREC](#)), in conjunction with the Department of Health. The National Office has established four National Research Ethics Committees (NREC) for the review of clinical trials. This procedure is set out in national legislation.

The respective roles are as follows:

- The HPRA is responsible for the scientific assessment (Part I) with input from the NREC on ethical matters.
- The National Office in conjunction with the NREC is responsible for the Part II assessment.
- The HPRA submits the single national decision for Ireland on a new application via CTIS, both on its own behalf and on behalf of the National Office and the NREC.

This coordinated procedure leads to a timely single national decision for Ireland on the scientific and ethical aspects of an initial clinical trial application.

Further information on the respective roles is provided in the national legislation listed in section 3.1 of this guide.

3.3 Communications

Communications with the HPRA and the National Office relating to a clinical trial undergoing evaluation, or an authorised clinical trial should be sent via CTIS. Documents or responses to RFIs should not be sent directly to the HPRA or the National Office, unless this is specifically requested (see sections 4 and 7 of this guide, Safety and Appeals, for exceptions. Appendix 1 includes the relevant email addresses if contact outside of CTIS is required).

3.4 Language

An application to Ireland, and all documents and communications before, during and after a clinical trial must be in the English language.

3.5 Investigational Medicinal Products and auxiliary medicinal products

3.5.1 Genetically modified organism

If an investigational medicinal product (IMP) proposed to be used in a clinical trial is a genetically modified organism, a separate application for a licence must be made to the Environmental Protection Agency (EPA) in Ireland. It is recommended that sponsors indicate in the clinical trial application cover letter if a risk assessment has already been submitted to the EPA or is in preparation.

For further details, refer to the EPA website at www.epa.ie.

3.5.2 Medical device

A clinical trial may involve a medical device in addition to a medicinal product. This may include: (i) one integral product combining a medicinal product and a medical device, or (ii) a clinical trial where the primary object of the study is a medicinal product used in conjunction with a medical device.

It is recommended that any medical devices used in the trial, including in vitro diagnostics (IVDs), are described in the cover letter together with a statement as to whether the medical devices are CE-marked for the intended use, in accordance with Annex I, Section 7(i) of the CTR.

For further guidance, refer to EudraLex Volume 10, 'Guidance Documents Applying to Clinical Trials', in particular the CTR Questions and Answers document (Question 1.12).

If the medical device used in a clinical trial is not CE-marked or is used outside its intended purpose, a clinical investigation or performance study (in the case of *in vitro* diagnostic medical devices) may be required. Please refer to the HPRA 'Guide to clinical investigations carried out in Ireland' or 'Guide to performance studies carried out in Ireland' for more information or contact the medical device department in the HPRA at devices@hpra.ie. The COMBINE programme is running a coordinated assessment pilot for clinical trials involving a performance study or clinical investigation, further details can be found on the [COMBINE webpage](#).

3.5.3 Free of charge

The sponsor must ensure the investigational medicinal products, and the auxiliary medicinal products used in the clinical trial, and any medical devices used for the administration of such products, are made available to subjects free of charge.

This requirement does not apply to a clinical trial conducted by a non-commercial sponsor, except in circumstances where the sponsor has obtained the products or devices referred to free of charge, in such cases, clinical trial subjects shall not bear any cost relating to such products or devices.

3.6 Labelling

Labelling requirements for IMPs and AxMPs are detailed in Chapter X and Annex VI of the CTR. A flowchart for labelling under CTR is provided in Annex 2 of the document 'Auxiliary Medicinal Products in Clinical Trials'. Labelling is required for all unauthorised IMPs, unauthorised AxMPs and authorised, modified AxMPs. Additionally, as per Article 67 of the CTR, specific circumstances may require clinical trial labelling to be provided for authorised IMPs or authorised AxMPs to ensure the safety of the subject or the reliability and robustness of data generated in a clinical trial.

The labelling text for IMPs and AxMPs, if any, must be in English. Other languages may be included; however, as far as possible, the full text for each language should be placed together on the label, rather than placing all language versions of each statement together.

3.7 Sponsors

As defined in the CTR, the 'sponsor' is the individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of a clinical trial. The sponsor does not need to be located in an EU Member State, but Irish

legislation requires that the sponsor, or the legal representative of the sponsor of a clinical trial in Ireland, must be established within the European Economic Area (EEA).

3.7.1 Delegation

The sponsor may delegate any or all of their trial-related duties and functions to another person or organisation. Any duties or functions delegated to a third party must be documented and specified in writing. The sponsor remains ultimately responsible for ensuring that the conduct of the trial and the data generated complies with the CTR and Irish legislation.

3.7.2 Co-sponsors

The CTR recognises that, in practice, there may be networks of researchers or research institutions which conduct a clinical trial jointly and may be considered co-sponsors. However, in order to uphold the sponsor responsibilities in a clinical trial as per the legislation and ICH-GCP, where a clinical trial has more than one sponsor, they should all be subject to the obligations of a sponsor under the CTR. They can be delegated specific responsibilities of the sponsor by contractual agreement. This may be particularly relevant for non-commercial (academic) sponsors conducting clinical trials in Ireland.

The investigator and the sponsor may be the same person. The responsibilities of a sponsor are described in chapter XI of the CTR, and in the Good Clinical Practice Guidance: ICH GCP E6 (R3).

3.7.3 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, such as safety reporting. Prior to taking that decision, the investigator or organisation needs to consider the resources and infrastructure necessary and must ensure systems and procedures are established that enable the role of sponsor to be fulfilled in a compliant manner.

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

The above describes some of the considerations relevant to non-commercial sponsors. For information on non-commercial sponsor system inspections, see section 8.9 of this guide.

A 'CTR Clinical Trial Protocol Template' is available to non-commercial sponsors on request by email to clinicaltrials@hpra.ie.

Non-commercial sponsors are recommended to request a pre-submission meeting prior to submitting the clinical trial application in CTIS by emailing clinicaltrials@hpra.ie.

3.8 Investigators

As defined in the CTR, the 'investigator' is an individual responsible for the conduct of a clinical trial at a clinical trial site. The NREC is responsible for determining the suitability of an investigator and the quality of the facilities at the clinical trial site.

Under Irish legislation, an investigator must be a registered medical practitioner or a registered dentist.

The investigator and the sponsor may be the same person.

The responsibilities of an investigator are described in chapter XI of the CTR, and in the Good Clinical Practice Guidance ICH GCP E6 (R3).

3.9 Subject information and the informed consent procedure

Irish legislation requires that the subject information and informed consent procedures should be in accordance with Chapter V of the CTR.

The national legislation introduced some changes to informed consent procedures, which are outlined below in brief; however, for completeness, the national legislation should be referred to for interpretation.

3.9.1 Legally designated representative for incapacitated subjects

In the case of an incapacitated subject, the definition of the 'legally designated representative' has been expanded to include family members, or persons with a personal relationship with the subject, or if either one of these is not available or is unwilling to provide consent, a medical practitioner who is primarily responsible for the medical treatment of the proposed subject. In all cases, the person or medical practitioner acting as a 'legally designated representative' should be able to provide the best interpretation of the will and preferences of the proposed subject.

3.9.2 Minors

In the case of a minor, a 'legally designated representative' who is a guardian should provide consent, but assent of the minor should also be obtained where a minor is capable of forming an opinion and assessing the information relevant to the clinical trial.

3.9.3 Emergency clinical trials

For clinical trials in emergency situations due to sudden life-threatening or serious medical conditions, informed consent for a subject to participate in the clinical trial may be obtained, and information on the clinical trial may be given, after the investigator's decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol, and if the conditions outlined in Article 35 of the CTR are fulfilled.

3.9.4 Simplified informed consent for 'cluster' trials

The Irish legislation makes provision for informed consent to be obtained by simplified means for clinical trials where groups of subjects rather than individual subjects are allocated to receive different IMPs. The IMPs must be used in accordance with the marketing authorisations, and the individual subject receives a standard treatment regardless of whether they accept or refuse to participate in the clinical trial, or withdraws from it, so that the only consequence of non-participation is that data relating to them are not used for the clinical trial. Such clinical trials, which serve to compare established treatments, if authorised in Ireland, can only be conducted in Ireland, that is, they are always mononational trials.

3.9.5 Prior interview – registered medical practitioner, dentist or nurse

Under Irish legislation, the interview performed prior to obtaining informed consent can be conducted by the investigator, or by a registered medical practitioner, registered dentist or registered nurse, who are deemed by the investigator as appropriate to conduct the interview, and this individual can take consent.

3.10 End of a clinical trial, temporary halt and early termination of a clinical trial and submission of the results

Article 37 of the CTR sets out the requirements and timelines for submitting notifications of the end of a clinical trial, temporary halt, or early termination, as well as for the submission of results via CTIS. The CTAG CTR Questions & Answers document, question 10, provides further guidance.

Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all MSCs, the sponsor shall submit a summary of the results of the clinical trial via CTIS. (The results should not be submitted directly to the HPRA).

The results comprise two summaries:

- A summary of the results;
- A summary written in a manner that is understandable to lay persons.

Further information on the contents of the summaries is set out in Annex IV and Annex V of the CTR. For information on the publishing of results, see 'Appendix on disclosure rules to the Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014' (www.ema.europa.eu).

3.11 Damage compensation system

A clinical trial must not be conducted in Ireland unless there is in place a policy of insurance or an indemnity scheme to provide compensation for any damage suffered by a subject resulting from participation in the clinical trial. The policy or scheme should be appropriate to the nature and the extent of the risk. As per the CTR, the sponsor should make use of any appropriate arrangements existing in Ireland, for example an insurance or guarantee or similar arrangement.

The NREC is responsible for reviewing the policy of insurance or indemnity scheme, and queries can be addressed to clinicaltrials@nrec.ie.

3.12 Fees

There will be a single fee per activity (e.g. new application or substantial modification) per MS. In Ireland, the fee should be paid to the HPRA, who then forward a portion of this fee to the National Office.

Proof of payment of the fee should be submitted with the clinical trial application to CTIS, along with a completed fee application form, which can be located on the [HPRA website](#).

No fees will be charged to sponsors of non-commercial or academic trials. Therefore, there is no fee requirement in CTIS. The HPRA and the National Office conduct a fee consultation every year, and the outcome is published on the HPRA website.

4 SAFETY REPORTING

The HPRA lead on clinical assessment of safety reports, and liaise with the National Office or NREC, as necessary. Further guidance on safety reporting is available in the CTAG CTR Questions & Answers document and CTCG Questions & Answers Safety Addendum (see references section 2 – EU Guidance).

4.1 Reporting suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) occurring during clinical trials undertaken in Ireland should be notified electronically by sponsors via the clinical trials module of the EudraVigilance database (EVCTM). SUSARs do not need to be reported directly to either the HPRA, or the NREC.

On specific request, the HPRA will assist non-commercial sponsors with electronic report submission to the EVCTM. For further detail refer to the safety reporting section under the HPRA supports in Appendix 1 of this guide.

Timelines for reporting of SUSARs differ depending on the category, fatal and life threatening SUSARs should be reported within 7 calendar days from first notification and all other SUSARs within 15 calendar days from first notification – as outlined in figure 1 below. For expedited reporting, the timelines start as soon as the sponsor has first knowledge of the minimum criteria required. The timelines also re-start if or when additional case information becomes available. For information on the circumstances relevant to unblinding of an investigational medicinal product, see Annex III, 2.5 of the CTR.

In situations where the HPRA is assisting non-commercial sponsors with electronic report submission to the 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.

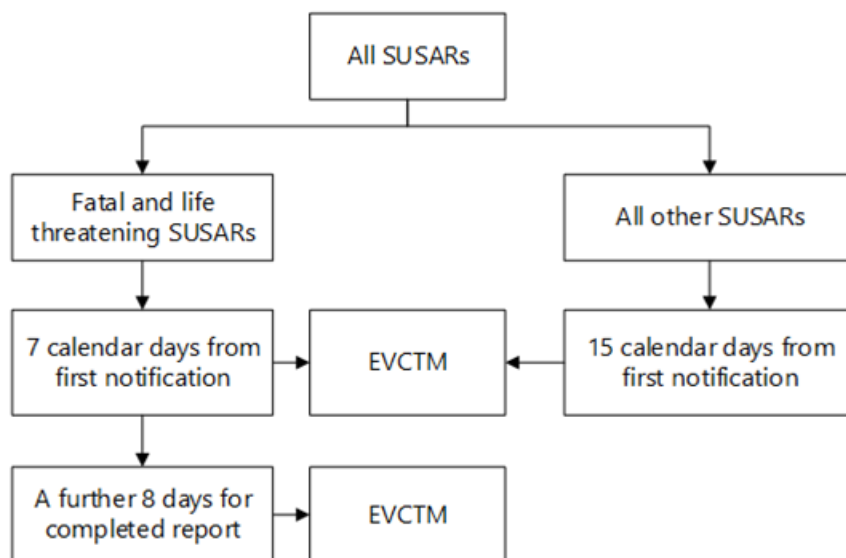


Figure 1: SUSAR reporting

4.2 Monitoring and reporting of adverse events

The sponsor is required to keep detailed records of all adverse events relating to a clinical trial that have been reported to them by the investigator(s) for that trial. The HPRA is entitled to request these records at any time.

4.3 Risk-adapted approach to safety recording and reporting

CTR Article 41 provides for risk-adapted safety recording and reporting in clinical trials. Where this approach is implemented, the protocol should include a robust justification supported by a trial-specific risk assessment.

Further guidance for sponsors is available in the CTCTG-endorsed guidance from the Danish Medicines Agency, 'The Danish Medicines Agency's guidance on risk-based recording and reporting of adverse events in clinical trials on medicinal products under Regulation (EU) No. 536/2014', and also in 'ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials'.

4.4 Annual Safety Report (ASR)

Sponsors are required to submit an annual safety report (ASR) via CTIS once a year, or on request. Guidance on the preparation of the report is provided in the ICH Guideline E2F and in EudraLex, Volume 10.

ASRs for clinical trials authorised under the CTR should be submitted through CTIS and should not be sent to the HPRA or the NREC.

A simplified ASR template is available on the HMA website for non-commercial sponsors conducting a single clinical trial on IMPs with a marketing authorisation in any of the EU/EEA Member States, where the applicable SmPC(s) is used as the reference safety information.

4.5 Unexpected events

The sponsor is required to notify the MSCs through CTIS of all unexpected events that affect the benefit-risk balance of the clinical trial, but are not SUSARs (CTR, Article 53). The notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

Unexpected events may relate to safety, or may relate to other events, examples include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

4.6 Urgent safety measures

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects (CTR, Article 54). The sponsor shall notify the MSs concerned, through CTIS, of the event and the measures taken. That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

4.7 Implementing Regulation on coordinated safety assessment in clinical trials

The EC Implementing Regulation (EU) 2022/20 outlines the legal framework for the implementation of coordinated safety assessment between MSs as mandated in Article 44 of the CTR. It defines the role of the safety assessing member state (saMS) and the process of SUSAR screening. The assessment of safety for active substances in clinical trials in more than one EU MS will be co-ordinated by the saMS, and the saMS may request further information following the identification of a safety concern in SUSAR or assessment.

5 SUPERVISION

5.1 Corrective measures

The HPRA and the National Office in conjunction with the NREC are responsible for the supervision of authorised clinical trials (see also section 8 GCP Inspections).

In response to breaches of the CTR, the HPRA is empowered under national legislation to take corrective measures such as:

- revoke the authorisation of a clinical trial;
- suspend a clinical trial;
- require the sponsor to modify any aspect of the clinical trial.

Unless immediate action is required, the sponsor and/or investigator will be given the opportunity to provide an opinion, within a seven-day time limit (calendar days).

The HPRA may consult with the National Office, the NREC and with other MSCs prior to taking a corrective measure. If a corrective measure is taken, the HPRA will notify the MSCs via CTIS.

For further information, please refer to the CTR and the national legislation.

5.2 Serious breaches

The CTR includes a requirement on the sponsor to report serious breaches through CTIS without undue delay and within seven calendar days of the sponsor becoming aware of the breach.

Serious breaches will be reviewed by the HPRA and, if necessary, by the National Office and the NREC. The HPRA will decide whether corrective measures are required. Regulatory actions may be taken by the HPRA if necessary. These include inspections and/or corrective measures. See the 'Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol' (EMA/698382/2021).

6 ARCHIVING

The sponsor and the investigators are required to retain the essential documents relating to a clinical trial for at least 25 years after its completion (CTR Article 58).

The essential documents are defined as those that individually and collectively allow effective supervision (monitoring by the sponsor and inspection by Member States), and this is referred to as the 'trial master file' (TMF).

These documents in the TMF 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 TMF should be archived appropriately to allow for supervision after the clinical trial has ended.

The national legislation requires that the medical files of trial subjects shall be retained for the maximum period of time permitted or required by the trial site.

7 APPEALS

A sponsor may appeal a single national decision to refuse a clinical trial application, or an application for substantial modification. The sponsor will be required to indicate whether the appeal relates to the Part I assessment or the Part II assessment, or both.

The sponsor wishing to make an appeal is required to submit the documentation to the HPRA within 28 days of the single decision. The HPRA and the National Office in conjunction with the NREC will review the appeal. A decision will be issued within 52 days.

An appeal is handled at national level, and not via CTIS. However, the HPRA will update the result of an appeal on CTIS, if relevant.

A fee may be charged.

Details are given in the national legislation, and further information is provided in the HPRA 'Guide to Refusals and Appeals'.

8 GOOD CLINICAL PRACTICE (GCP) INSPECTIONS

8.1 Introduction

GCP is an international, ethical, scientific and quality standard for the conduct of trials that involve human participants. Clinical trials conducted in accordance with this standard will help to assure that the rights, safety and well-being of trial participants are protected; that the conduct is consistent with the principles that have their origin in the Declaration of Helsinki; and that the clinical trial results are reliable. The term 'trial conduct' includes processes from planning to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate.

The regulations require that all clinical trials covered by the provisions of the regulations, including bioavailability and bioequivalence studies, be designed, conducted and reported in accordance with the principles of GCP.

To supervise compliance, clinical trials authorised under the CTR may be inspected by the HPRA to determine if they are in compliance with GCP, the relevant clinical trial permission, the trial protocol and applicable legislation and guidance.

Inspections are conducted by the GCP/PV inspection team, who may be accompanied by relevant experts where required. Inspections are typically conducted on a routine basis or may arise as a result of a specific trigger. Sites for routine inspections are selected using a risk-based approach.

A request to inspect a trial may also be received from the Competent Authority of another EU member state or from the EMA through the Committee for Human Medicinal Products (CHMP). If requested, the HPRA may conduct such inspections in collaboration with inspectors from other EU member states. This may involve inspection of sites internationally, including trial sites in third countries outside of the EU where required. Where the HPRA participates in CHMP requested inspections, they are conducted according to both HPRA and relevant EMA inspection procedures (see References).

8.2 Types of GCP inspections

Any site involved in a clinical trial may be subject to inspection, including the investigator sites, any laboratory used for clinical trial analyses and the sponsor's premises. Sites which are acting under arrangements with a sponsor or investigator to perform some or all the functions of the sponsor or investigator, such as contract research organisations or clinical research facilities, may also be subject to GCP inspection.

Inspections may be study specific and focus on verifying the compliance of a single clinical trial, or they may be broader systems-based inspections. Typically, investigator site inspections are study specific, while inspections of sponsors or clinical research facilities may be used to broadly examine systems and processes in place to support clinical trials generally. The scope of the inspection will be communicated in advance (see further information below).

Inspections may be carried out on any of the following occasions:

- Before, during or after the conduct of clinical trials.
- As part of the verification of applications for a marketing authorisation.
- As a follow-up to the granting of authorisation.

Inspections may be announced or unannounced, however notice is generally provided. It is important to note that the legal framework does not distinguish between academic/non-commercial versus commercial trials, be they run through a clinical research facility or other. Therefore, the HPRA applies the same standards to all GCP related inspections. Please see section 8.9 of this guide for advice for non-commercial/academic sponsors on GCP inspections.

8.3 Procedure for GCP inspections

The typical procedure for the conduct of routine national GCP inspections is outlined in the following sections with a visual representation of the process in figure 2 below. EMA requested inspections will follow a similar process but are conducted according to different timelines.



Figure 2: Routine national GCP inspection process

8.4 Notification

In general, the sponsor of a clinical trial will be notified 4-6 weeks prior to the proposed inspection date and asked to confirm availability. In relation to for cause or triggered

inspections, a shorter notice period may be provided. The notification will identify the clinical trial to be inspected, if applicable, and the proposed site(s). It will also outline the scope and the planned number of inspection days. The notification will include an initial list of pre-inspection requests for information and documentation that is to be provided to the HPRA in advance, to aid with preparation. This may include:

- Participant status per trial site (number randomised, drop-out rate, and number of serious adverse events reported per site).
- Copies of sponsor/investigator 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.
- CV of principal investigator and key members of the study team, and a copy of the delegation log.
- Arrangements for direct access to any computerised systems upon which trial data or essential documents are stored.
- Logistical aspects for arranging the inspection.
- Any other documentation deemed necessary by the inspectors.

Further pre-inspection document requests may follow after the initial documents requested are reviewed. An inspection plan, outlining the units to be inspected and the schedule of meetings to be held with the investigator and/or sponsor personnel, will be provided to the inspectee at least one week prior to the inspection.

8.5 Conduct

The duration of the inspection and the number of inspectors present on an inspection will vary depending on the complexity of the clinical trial and activities conducted at the site. Typically, they are scheduled for 3-5 days. Where appropriate, inspections may also be conducted remotely.

The activities conducted during an inspection, including the type of documentation reviewed, will vary depending on the type of inspection and the scope. However, inspections usually consist of an opening meeting, document review, interview sessions, tour of facilities and a closing meeting.

The scope and activities examined during some of the more common types of GCP inspections undertaken by the HPRA are outlined below. This list is not exhaustive.

Investigator site inspections may include:

- Legal and administrative aspects

- Communication with the Ethics Committee
- Communication with the Regulatory Authority
- Other communications
- Organisational aspects
 - Implementation of the trial at the investigator site
 - Facilities and equipment
 - Management of biological samples
 - Organisation of the documentation
 - Monitoring and auditing
 - Use of computerised systems
- Informed consent of trial participants
- Review of the trial participant data
- Protocol compliance
- Adverse event and serious adverse event reporting
- Management of the investigational medicinal product(s)

Sponsor (systems) inspection may include:

- Organisation and personnel
- Facilities and equipment
- Use of computerised systems
- Sponsor/CRO operating procedures
- Setup, conduct and termination of the clinical trial
- Monitoring and deviation management
- Investigational Medicinal Product management
- Sample management
- Ongoing safety evaluation and safety reporting
- Data handling and clinical trial report
- Clinical trial documentation and archiving
- Audit and quality assurance system
- Delegation of duties

Sponsor (specific clinical trial) inspection may include:

- Set up, conduct and termination of the clinical trial
- Monitoring and deviation management
- Investigational Medicinal Product management
- Safety reporting

- Ongoing safety evaluation
- Data management and use of computerised systems
- Statistical analysis
- Reporting of clinical trial results
- Clinical trial documentation and archiving
- Quality management system/audit

8.6 Closing meeting

A closing meeting is typically held on the last day of the inspection, where the inspectors will provide a verbal overview of the deficiencies identified. Feedback given at the closing meeting is preliminary in nature as inspection reports are subject to internal peer review at the HPRA before they are finalised and issued.

A definition of the deficiency classification used will also be provided, any questions related to the findings will be addressed, and the timelines for follow up activities will be outlined. Findings are classified according to the criteria below.

- Critical:** Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.
- Major:** Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles.
- Minor:** Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data.

8.7 Compliance Regulatory Group

If significant deficiencies are identified which are potentially critical in nature, the case is referred to the HPRA's Compliance Regulatory Group (CRG) for consideration. The CRG is a cross-functional group chaired by the Director of Compliance, and for GCP matters would typically be attended by the relevant Section Manager, GCP/PV Inspection Manager and relevant personnel from other relevant departments within the HPRA. The group agree on the classification of the serious deficiencies identified and consider if any further regulatory action may need to be proposed.

8.8 Reporting and follow-up

A written report outlining deficiencies observed during the inspection will be issued to the inspectee within three weeks of the last day of the inspection.

The inspectee will be requested to provide a response to the deficiencies outlined in the report within approximately three weeks of receipt. The report will outline the deadline for response and will contain a template to assist with responses. A response for each finding should be provided, outlining a root cause analysis of the deficiency, further assessment if required, and a proposal for corrective and preventative actions (CAPA). Specific actions are expected to be provided, including deliverables, persons responsible and a timeframe for completion.

The responses will be reviewed by the inspection team to determine whether or not they are acceptable to address the deficiencies and to prevent reoccurrence. The inspectors will routinely send follow up queries or request further clarification before the responses are deemed acceptable. On receipt of acceptable responses to the inspection report, the inspection can be closed, and a final inspection report is issued.

The HPRA is required to upload inspection reports to CTIS, which will be available within the EU regulatory network.

8.9 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 a non-commercial setting, it is typical 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 GCP E6, 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 GCP E6, 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, 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/National Office or and/or NREC/investigators and ASR 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.

- **Non-compliance and serious breaches:** Sponsor procedures to deal with significant and/or persistent non-compliance, including processes for performing root cause analysis and implementing corrective and preventative actions and the reporting of serious breaches, 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 essential records for the conduct of a clinical trial in the clinical trial master file 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.

9 MANUFACTURE AND/OR IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

Investigational medicinal products (IMPs) used in clinical trials must be manufactured in accordance with the requirements of the 'EU Guidelines on Good Manufacturing Practice for Investigational Medicinal Products' (volume 4 of the Rules Governing Medicinal Products in the European Union). Each company located in the EEA or Northern Ireland that is responsible for any manufacturing activity related to the dosage form, packaging or batch certification of the IMP must have an MIA. The MIA is issued by the HPRA for manufacturing sites located in Ireland and should include within its scope the specific manufacturing activities which are relevant for the IMP concerned.

With the exception of IMPs or AxMPs supplied by an authorised manufacturer in Northern Ireland, IMPs or AxMPs that are coming from a third country (i.e. outside the EEA) must be imported into Ireland by a site holding an MIA that includes third-country importation within its scope. The Qualified Person certifying the batch must be satisfied that any third country site involved in the manufacture or packaging of the IMP or AxMP operates according to a standard of GMP at least equivalent to EU GMP for IMPs. Each imported batch of an IMP or AxMP must be certified before release by the Qualified Person of the manufacturer named in the clinical trial application as responsible for batch release.

The HPRA requires sites of batch release to list all manufacturing sites involved in the supply chain as contract manufacturers on their Manufacturer's / Importer's Authorisation (MIA). MIA

holders should refer to the HPRA Guide to New Applications and Variations to Manufacturer's Authorisations on www.hpra.ie when submitting new applications or variations to add or remove contract manufacturers.

9.1 Manufacture/importation of authorised investigational medicinal products and authorised auxiliary medicinal products

As per Article 2 (9) and (10) respectively, of the CTR, an 'authorised' investigational medicinal product or an 'authorised' auxiliary medicinal product is a medicinal product authorised for supply on the Irish market or another market in the EEA, irrespective of changes to the labelling of the medicinal product used as an IMP or AxMP, respectively.

When authorised IMPs and AxMPs are additionally labelled or re-labelled for use in clinical trials, even though the operation is not considered a modification of the product, the labelling/relabelling activities are manufacturing operations. Therefore, information regarding the responsible organisation for performing the additional labelling or re-labelling activities should be included in the clinical trial application, where appropriate, in a simplified IMPD or AxMPD.

Importation of any authorised medicines must be performed by the holder of an MIA authorised under Article 40 of Directive 2001/83/EC. If an authorised medicine, which has been certified for release to a market in the EEA, undergoes any modification for its use as an IMP or AxMP in the context of a clinical trial, e.g. packaging or repackaging, then this activity must be conducted to a standard of GMP at least equivalent to that applied to manufacture of IMPs, i.e. Commission Delegated Regulation (EU) 2017/1569. The manufacturer performing modification of the authorised medicine, if located in Ireland, must hold an MIA issued by the HPRA, which authorises the manufacturing activity under Article 61 of the CTR.

9.2 Exemptions from the requirement for an MIA

Under Article 61(5), the CTR provides for an exemption from the requirement for an MIA for certain specified manufacturing processes when these are carried out in hospitals, health centres or clinics that are participating in the same clinical trial. The HPRA has implemented a registration scheme for processes carried out under Article 61(5). Any re-labelling or re-packaging to be performed according to Article 61(5) (a) should be addressed in the cover letter of the application on CTIS.

Processes under Article 61(5) should be carried out in accordance with appropriate and proportionate requirements. Following registration, the HPRA has implemented a risk-based inspection programme for these processes. For further information, refer to the Guide to

Registration of Processes under Article 61(5) of the Clinical Trial Regulation available on the HPRA website.

9.3 Inspection of manufacturers and importers and Article 61(5) processes

9.3.1 Inspection of authorised manufacturers in Ireland

The HPRA conducts routine GMP inspections of all authorised manufacturers in Ireland and these are carried out at a frequency based on risk associated with the site. Further information on inspections relating to authorised manufacturers is available on the HPRA website.

9.3.2 Inspection of processes on the Article 61(5) Register

The HPRA may inspect processes carried out in hospitals, health centres or clinics that are included on the Article 61(5) Register. Inspections will be conducted using a risk-based approach. The inspection procedure (inspection notification, conduct of inspection, reporting on inspection and responding to the inspection report) will be similar to that described on the HPRA website for inspection of authorised manufacturers with the exception that a certificate of Good Manufacturing Practice will not be issued following a successful inspection.

9.3.3 Inspection of IMP contract manufacturers located in third countries

Under Article 17 of the Commission Delegated Regulation (EU) 2017/1569, the HPRA may conduct inspections at IMP manufacturing sites located in third countries. It is not planned to implement routine inspection of all third country manufacturers but rather to select sites for inspection based on risk.

10 ENFORCEMENT

The HPRA is the responsible body for enforcement of the CTR and national legislation pertaining to clinical trials 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 legislation.

11 CLINICAL TRIALS WITH DECENTRALISED ELEMENTS

Clinical trials are increasingly using procedures outside the traditional research site or using digital tools. The [EMA/HMA Recommendation Paper on Decentralised Elements in Clinical Trials](#) paper highlights the roles and responsibilities of the sponsor and investigator, the electronic consent form, delivery of the investigational medicinal product, procedures at the participant's home, data processing and monitoring in a decentralised clinical trial.

The appendix of the recommendation paper contains an overview of national provisions, including those relevant to Ireland, and provides answers to the questions relating to the context and general recommendations outlined in the recommendation paper.

APPENDIX 1 HPRA SUPPORTS

The HPRA offers a number of supports to sponsors and investigators, which are outlined below.

Clinical trials queries

- General queries on clinical trials can be sent to clinicaltrials@hpra.ie.
- Queries on authorised or clinical trial applications under evaluation should be sent to CTReg@hpra.ie (however assessment correspondence is managed within CTIS, e.g. the RFI and sponsor response to RFI).
- Queries on ethical aspects should be sent to clinicaltrials@nrec.ie.
- CTIS related queries can be directed to [EMA CTIS Service Desk](#).

Regulatory and scientific advice

The HPRA provides regulatory and scientific advice on clinical trial developments and/or protocols. Please refer to <https://www.hpra.ie/regulation/human-medicine/marketing-authorisation-holders/national-scientific-and-regulatory-advice>.

Clinical Trial Classification Requests

The HPRA provides advice on whether a planned clinical study or trial falls under the scope of the CTR. The request must be submitted to the HPRA via email (clinicaltrials@hpra.ie) and must include the trial protocol and information on the investigational medicinal product to be tested (e.g. SmPC where applicable). If the protocol is not complete, a synopsis, which includes the purpose, endpoints, and description of how they are achieved should be provided.

It is recommended to consult Annex I of the CTAG CTR Questions & Answers document before submitting the request, as it provides a decision tree to help determine whether a study falls within the scope of the CTR.

If there is doubt whether the substance to be tested is a medicinal product or not, it is recommended that a separate request for classification of a human health product is submitted to the HPRA Borderline Products Committee. Please refer to the [HPRA Classification requests and innovation support webpage on the HPRA website](#).

Pre-submission meetings

For innovative trials including Advanced Therapy Medicinal Product (ATMP) clinical trials and trials using genetically modified organisms, or for clinical trials with non-commercial (academic) sponsors, the HPRA recommends that the sponsor requests a pre-submission meeting to discuss the potential clinical trial application.

This service is free of charge for clinical trials to be conducted in Ireland. The meeting should be requested well in advance of the intended application date. Please contact clinicaltrials@hpra.ie.

Protocol template

A 'CTR Clinical Trial Protocol Template' is available to non-commercial sponsors intending to conduct clinical trials in Ireland. Please email clinicaltrials@hpra.ie.

Safety reporting – non-commercial sponsors

Upon specific request, the HPRA will assist non-commercial sponsors with electronic report submission to EVCTM. In such cases, a request should be submitted to medsafety@hpra.ie at the time of submission to facilitate the timely completion of arrangements.

Advice for non-commercial (academic) sponsors

See sections 3.7.3 and 8.9 of this guide.

Advice on GXP activities

To assist potential applicants for GXP authorisations/registrations to understand the requirements that must be fulfilled in order to be compliant we refer to the HPRA Guide-to-Scientific and Regulatory Advice for GXP Activities on the HPRA website www.hpra.ie. This includes review of plans for new manufacturing facilities.

Advice can also be provided, on request, to existing authorisation holders that are, for example, considering expansion or alteration of premises, installation of new or revised processes, etc.

Sponsors and/or investigators involved in the conduct of clinical trials of medicines in humans seeking advice on the interpretation of GCP guidelines for layout of facilities should email compliance@hpra.ie.

APPENDIX 2 REFERENCES

1. Legislation

- Regulation 536/2014: https://ec.europa.eu/health/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en
- Commission Implementing Regulation (EU) 2022/20, setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trial: https://eur-lex.europa.eu/eli/reg_impl/2022/20/oj
- Commission Delegated Regulation (EU) 2017/1569 specifying principles and guidelines for good manufacturing practices and arrangements for inspections: https://eur-lex.europa.eu/eli/reg_del/2017/1569/oj
- European Union (Clinical Trials) Regulations 2022 (S.I. No 99/2022), implementing the CTR, and setting out the responsibilities of each of the stakeholders, and the powers of the HPRA ('the Authority') at national level; <https://www.irishstatutebook.ie/eli/2022/si/99/made/en/print>
- European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022 (S.I. No 41/2022), establishing the National Office for Research Ethics Committees (hereafter 'National Office') and the National Research Ethics Committees for clinical trials; <https://www.irishstatutebook.ie/eli/2022/si/41/made/en/print>
- Medicinal Products (Control of Manufacture) (Amendment) Regulations 2022 (S.I. No 43 of 2022), amending the Medicinal Product (Control of Manufacture), Regulations 2007 (S.I. No 539/2007): <https://www.irishstatutebook.ie/eli/2022/si/43/made/en/print>

2. EU guidance

Note: The documents and links listed below may be updated from time to time; therefore, it is recommended to refer to the most up to date version.

- Transition: [2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf](https://www.hma.eu/2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf) (hma.eu)
- Transparency: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf
- EudraLex - Volume 10 - Clinical trials guidelines: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en
- Revised CTIS Transparency Rules: https://www.ema.europa.eu/en/documents/other/revised-ctis-transparency-rules_en.pdf
- CTAG CTR Questions & Answers document: https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en.pdf

- CTEG Q&A on Safety Addendum: https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTEG/CTEG-QandA-on-Safety-Addendum-V3.pdf
- Risk proportionate approaches in clinical trials: [2017_04_25_risk_proportionate_approaches_in_ct_0.pdf](https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTEG/2025_08_CTEG_Simplified_template_ASR_final.docx)
- The Danish Medicines Agency's guidance on risk-based recording and reporting of adverse events in clinical trials on medicinal products under Regulation (EU) no. 536/2014: <https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/safety-reporting-during-clinical-medicinal-trials/~media/8E1AFBB2C13C47E19D088765F917116C.ashx>
- CTEG simplified ASR template for non-commercial sponsors: https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTEG/2025_08_CTEG_Simplified_template_ASR_final.docx
- Reflection paper on risk-based quality management in clinical trials: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf
- Serious breaches: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-5362014-or-clinical-trial-protocol_en.pdf
- EMA inspection procedures: [EMA inspection procedures](https://www.ema.europa.eu/en/inspection-procedures).
- EMA Organisation Management Service (OMS): <https://www.ema.europa.eu/en/human-regulatory/research-development/data-medicines-iso-idmp-standards/spor-master-data/organisation-management-service-oms>
- EMA Clinical Trials highlights: <https://www.ema.europa.eu/en/news-and-events/publications/newsletters#clinical-trials-highlights-12425>
- Recommendation paper on decentralised elements in clinical trials: https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf

3. Clinical Trials Information System (CTIS)

- EMA Clinical Trials Information System: training and support: <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/clinical-trials-information-system-ctis-training-support>
- EMA Clinical Trial Information System (CTIS) – Sponsor Handbook: https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_en.pdf

4. Department of Health

<https://www.gov.ie/en/organisation/departments/departments-of-health/>

5. National Office for Research Ethics Committees

<https://www.nrecoffice.ie/>

6. Others

- Clinical Trials Coordination Group (CTCG): <https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html>
- EMA Account Management: <https://register.ema.europa.eu/identityiq/login.jsf>
- ICH guideline E2F on development safety update report: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-26.pdf
- ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e19-selective-approach-safety-data-collection-specific-late-stage-pre-approval-or-post-approval-clinical-trials-step5_en.pdf

7. IMPs and AxMPs

- Auxiliary medicinal products in clinical trials GMP for IMPs: Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014
- Template for the qualified person's declaration equivalence to EU GMP for Investigational Medicinal Products manufactured in third countries: PDF version (May 2013)
- Batch certificate template: Template for IMP batch release (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials)
- Union Basic Format for Manufacturer's Authorisation (June 2013)
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017)

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008)