MALTA
MEDICINES
AUTHORITY

GUIDANCE NOTES ON CLINICAL TRIALS CONDUCTED UNDER THE CLINICAL TRIALS REGULATION (CTR) IN MALTA

Ref No: GL-CT01.12

February 2024
Post- Licensing Directorate

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1. INTRODUCTION

No person shall start a clinical trial in Malta unless the Health Ethics Committee has issued a favorable opinion and the Licensing Authority has authorized it.

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 [hereinafter referred to as "the CTR"] is the law that applies to all clinical trials conducted in the European Union (including in Malta).

The CTR was adopted on 16 April 2014 and became applicable on 31 January 2022. The CTR replaces the previous Maltese legal framework and may be accessed on: *https://eur-lex.europa.eu/homepage.html*

The Regulation strives for a greater level of harmonisation of the rules for conducting clinical trials throughout the EU. It introduces an authorisation procedure based on a single submission via a single EU portal (known as the Clinical Trials Information System [CTIS]), an assessment procedure leading to a single decision, rules on the protection of subjects and informed consent, and transparency requirements. The Regulation also aims to facilitate the conduct of multinational clinical trials in the EU.

2. SCOPE

These guidance notes have been prepared to help applicants when submitting applications, amendments and notifications for clinical trials to run under the Clinical Trials Regulation to the Medicines Authority, via the Clinical Trials Information System (CTIS).

These guidance notes should be read in conjunction with EU and national legislation, and EC and EMA guidelines. Trials of medicinal products in humans must be conducted in accordance with the Good Clinical Practice. Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products.

As of 31 January 2023, all initial clinical trial applications in the European Union (EU)/European Economic Area (EEA) must be submitted through CTIS. In order to obtain such an authorisation from the Medicines Authority to start a clinical trial, a clinical trial application shall be submitted to the Medicines Authority via CTIS.

The CTR applies to clinical trials on medicinal products for human use (including both commercial and non-commercial trials). It does not apply to non-interventional studies. The regulations do not refer to foods, food supplements, cosmetics or medical devices.

The CTR provides a definition of a "clinical study", of a "clinical trial" and of a "low-intervention clinical trial" (see article 2.2 and 2.3 of the CTR).

3. DEFINITIONS

Article 2 of the CTR provides the definition of important terms.

Clinical study

A clinical study means any investigation in relation to humans intended:

- to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; and/or
- to identify any adverse reactions to one or more medicinal products; and/or
- to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products.

Clinical trial

A clinical trial means a clinical study which fulfils *any* of the following conditions:

- the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
- the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;
- diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Low-intervention clinical trial

A low-intervention clinical trial means a clinical trial which fulfils *all* of the following conditions:

- the investigational medicinal products, excluding placebos, are authorised; and
- according to the protocol of the clinical trial,
    - the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
    - the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
- the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Applicant

The legal applicant i.e., sponsor or person / organisation authorized by the sponsor or legal representative of

the sponsor. The applicant may be a non-commercial sponsor. The sponsor takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial.

Health Ethics Committee

An independent body, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to recruit and inform trial subjects and obtain their informed consent.

The Health Ethics Committee in Malta is a separate entity from the Medicines Authority. More information on the Health Ethics Committee is available at
https://healthservices.gov.mt/en/appbodies/hec/Pages/hec.aspx

Address:

Health Ethics Committee
Directorate for Health Information & Research
95, Gwardamangia Hill,
Pieta' - Malta
PTA 1313

Email: *hec@gov.mt*

Member State

A State which is a member of the European Union and shall also include Iceland, Norway and Liechtenstein.

The Community

The European Community and the European Economic Area.

4. SPECIFIC GUIDANCE

4.1 TRANSITION

From the 31 January 2023 onwards, all new clinical trial applications must be submitted under the CTR via the Clinical Trials Information System (CTIS).

By 31 January 2025, clinical trials authorised under the directive (Directive 2001/20/EC) must either have ended in the EU/EEA or have been transitioned to the CTR framework.

For further information on transitioning clinical trials that were authorised under the directive to the CTR, refer to EudraLex, Volume 10, 'Guidance Documents Applying to Clinical Trials, Questions and Answers available from: *https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en*

4.2 CLINICAL TRIALS INFORMATION SYSTEM (CTIS)

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 EC and the public have access to different aspects of the system comprising of restricted and secured workspaces and a publicly accessible website.

The CTIS facilitates the harmonisation of both the submission and assessment of clinical trials across the European Union and acts as the primary submission portal for all applications and for communications between sponsors and MSs. Submission of clinical trial information outside of CTIS are not allowed.

In order to access the CTIS Sponsor workspace, a user needs to have an active EMA Account.

For detailed information on the CTIS system including sponsor training and registration, please visit *https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-training-support*

A questions and answers document on CTIS is available from *https://euclinicaltrials.eu/guidance-and-q-as/*

The CTIS sponsor workspace is accessible from: *https://euclinicaltrials.eu/*

4.3 EUDRACT DATABASE

EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) is the database for all interventional clinical trials on medicinal products submitted to the National Competent Authorities (NCAs) of the European Union (EU)/European Economic Area (EEA) from 1 May 2004 until 30 January 2023 under Directive 2001/20/EC.

The use of the EudraCT database is now limited to:

- the performance of amendments to EU/EEA Clinical Trial Applications for which the initial submission was done before 31 January 2023
- the upload of third country files of trials conducted exclusively outside of the EU/EEA that are part of a Paediatric Investigation Plan (PIP) and/or in scope of Article 46 of the Paediatric Regulation (EC) 1901/2006 (so called "third country files")
- the update of EudraCT trial statuses by National Competent Authorities
- the submission of results of EudraCT trials by sponsors

Sponsors must transition their trials to CTIS in case:

- their EudraCT trial is going to be conducted in additional EU/EEA member state(s), to which a EudraCT Clinical trial Application was not submitted before 31 January 2023 (this is considered a new trial application for this member state)
- their EudraCT trial completion date is expected to be after 30 January 2025

4.4 CLINICAL TRIAL APPLICATIONS

A Clinical trial application (CTA) is a request made by the sponsors to the Member States Concerned (MSCs) for the authorisation to perform an action related to CTs conducted in the EU. These actions can include the authorisation to conduct a new CT, to extend an existing CT to another MSC territory, or to perform a substantial modification (SM) to a previously authorised CTA.

Depending on the number of Member States concerned by the application, initial CTAs can be for mono-national clinical trials or as multinational trials.

In the case of multinational trials, the sponsor decides which MSs to include in their application. These are referred to as 'Member States Concerned' (MSCs). The sponsor can also nominate an MSC to be the lead or 'Reporting Member State' (RMS) at the time of submission of an initial application dossier. The RMS status is assigned to an MSC after the completion of the RMS selection tasks by all MSCs.

In the case of mono-national trials the MSC will be automatically appointed to be the RMS after the submission of the application dossier.

There are 2 parts in the clinical trial application:

- 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 [in the case of multinational trials]
- 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.

Sponsors have the option of submitting their initial application in full (i.e., Part I and II) or in two phases (partial submissions). In the case of part I only applications sponsors will need to wait for the RMS/MSC to submit the conclusion of the assessment to part I (reporting date) before they can submit part II. After the reporting date, the sponsor has two years to complete their application with the part II to obtain a decision for the trial. Failure to do so within this period leads to the lapse of the application

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.

An authorisation of a clinical trial granted by the Medicines Authority does not imply approval of the development programme of the tested investigational medicinal product (IMP).

Assessment of an initial CTA includes the whole process of evaluation: validation, assessment (part I and part II or part I only), and decision. The CTR establishes an overall timeline of 60 days for the Member States to evaluate an Initial application. This deadline may be extended in case that Requests for Information (RFIs) are raised by a Member State Concerned (MSC) throughout the evaluation process.

4.4.1 SUBMITTING THE CLINICAL TRIAL APPLICATION

To create an application in CTIS, users have to be registered and given the appropriate roles and permissions within CTIS. Organisations have to be registered in the organisation management system and medicinal products have to be registered in the medicinal product dictionary.

If the sponsor organisation is registered in EMA's Organisation Management Service (OMS), sponsors can retrieve organisation details in CTIS to populate applications for clinical trials. If the sponsor organisation is not registered yet in the OMS, the sponsor should register it via the SPOR data management services first. Guidance is available on the SPOR website under OMS: Documents accessible via *https://spor.ema.europa.eu/omswi/#/viewDocuments.*

During the initial CTA creation process a unique EU CT number is generated and will be associated with that clinical trial.

The application form should be submitted in English. Documentation attached to the application should be submitted in English and/or Maltese. Documents given to patients should be translated in **both** English and Maltese. This includes the Informed consent form and Subject information leaflet.

4.4.2 VALIDATION OF THE DOCUMENTATION RECEIVED

The documentation received via CTIS will be subject to a validation check in order to ensure that all information requested is submitted correctly. The validation starts as soon as the application dossier is submitted. If additional information / clarification is required, a request for information (RFI) is raised. In

case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application.

4.4.3 ASSESSMENT OF THE DOCUMENTATION RECEIVED

Clinical trial applications shall be subject to scientific and ethical review and shall be authorised in accordance with the CTR. The Medicines Authority is concerned with assessment of Part 1. Assessment follows successful validation. During the assessment, Requests for Information (RFIs) may be raised. Following the assessment and the conclusions of Part I and Part II assessment have been submitted, a decision is issued through CTIS.

The Medicines Authority reserves the right to reject the application and gives the reasons in writing for so doing. In this case, the applicant may appeal only once and within twenty (20) calendar days of the notification of the negative decision from the Medicines Authority. Further documentation may be presented during this appeal. An appeal is handled at national level, and not via CTIS. However, the Medicines Authority will update the result of an appeal on CTIS, if relevant.

4.5 CLINICAL TRIAL MODIFICATION

During the trial, the sponsor may modify the clinical trial. Under the scope of the CT Regulation, an amendment to a clinical trial can be:

- a substantial modification (SM)
- a non-substantial modification

A SM is any change to any aspect of a CT, which is made after the notification of a decision on a previously submitted application and which is likely to either:

• Have a substantial impact on the safety or rights of the subjects; or
• On the reliability and robustness of the data generated in the CT.

In all cases, a modification is regarded as 'substantial' when one or both of the above criteria are met.

In principle, it is the responsibility of the sponsor to judge whether a modification is to be regarded as 'substantial' or not. This judgement is to be made on a case-by-case basis considering the above criteria.

For a non-exhaustive list of substantial modifications, non-substantial modifications and non-substantial modifications relevant to the supervision of the clinical trial please consult Annex IV of the Questions and Answers Document – Regulation (EU) 536/2014 [Version 5 (January 2022)]. Please see: *https://health.ec.europa.eu/latest-updates/questions-and-answers-document-regulation-eu-5362014-version-5-january-2022-2022-02-01_en*

4.5.1 EVALUATION OF SUBSTANTIAL MODIFICATIONS

The evaluation process of SM CTAs is established in the Regulation (EU) No 536/2014 on Clinical Trials (CT Regulation). This process includes Validation, Assessment of Part I and/or Assessment of Part II, and

the Decision. Some SMs may concern Part I only, Part II only, or both, depending on the scope of the modification.

The Medicines Authority reserves the right to reject the SM application and gives the reasons in writing for so doing. In this case, the applicant may appeal only once and within twenty (20) calendar days of the notification from the Medicines Authority. Further documentation may be presented during this appeal. An appeal is handled at national level, and not via CTIS. However, the Medicines Authority will update the result of an appeal on CTIS, if relevant.

4.6 END OF CLINICAL TRIALS

The sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through a notification in CTIS. This notification must be made within 15 days from the end date.

4.7. CONTROL OF CLINICAL TRIALS – INSPECTION

Article 2(31) of the Clinical Trial Regulation (CTR) refers to an inspection as the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the clinical trial site, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect. An inspection has the aim to evaluate a clinical trial in terms of its compliance with the CT Regulation.

The Medicines Authority carries out, on a risk-based approach, routine inspections for clinical trials of medicinal products in Malta. The inspections are partly performed by visiting the doctors carrying out the clinical part of trials, and partly by visiting the companies that are partially or entirely responsible for managing the trials, depending on the particular clinical trial. In addition, inspections can be made by visits to other parties involved in a trial, such as hospital pharmacies and laboratories.

The purpose of the inspections is to control whether the clinical trials are carried out in compliance with EU clinical trial legislation and the authorised trial protocol. Trials of medicinal products must be carried out in accordance with the international code on good clinical practice. Therefore, it is also controlled whether this code of practice is complied with.

The inspections are an attempt to ensure the credibility of the data registered (what does the trial show?) as well as the safety for the trial subjects participating.

The selection of trials for inspection can cover all types of trials to the extent possible. This means the different phases (phases I-IV), single and multi-centre trials, hospitals and general practices or other specialist practices as well as the different medical specialties.

Inspections may be triggered. These inspections that are carried out by the inspectors following the need to verify and address specific concerns, issues identified for the trial and/or the site.

A written report outlining deficiencies observed during the inspection will be issued to the inspectee through CTIS. The Medicines Authority is required to upload inspection reports to CTIS, where they are publicly accessible (CTR Article 78 (6) and 81 (4)).

4.8 CLINICAL TRIALS AND ADR REPORTING (SUSARS & ASRS)

The legal obligations of the sponsors of clinical trials are specified in the Clinical Trials Regulation 536/2014.

Further guidance on the requirements of sponsors and investigators is outlined in the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" issued by the European Commission. This guidance can be obtained from EudraLex - Volume 10 Clinical trials guidelines, Chapter II: Safety Reporting hosted the following website: *https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en*

The sponsor of the study is responsible for reporting SUSARs in Eudravigilance. The sponsor needs to register with Eudravigilance. More information on the steps to be followed, can be found at *https://eudravigilance.ema.europa.eu/human/HowToRegister.asp.* On specific request, the Medicines Authority will assist non-commercial sponsors with electronic report submission to the EVCTM. In such cases, a request should be submitted to info.medicinesauthority@gov.mt at the time of submission of the CT application to facilitate timely completion of arrangements.

SUSARs should be submitted electronically via EudraVigilance in E2B(M) format, directly to EudraVigilance clinical trials module (EVCTM). Information regarding the testing of such electronic submission can be obtained from the EMA website on Eudravigilance

SUSARs arising from clinical trials conducted in Malta and from multi-centre clinical trials which include Maltese centres should be submitted electronically by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM) using message receiver identifier EVCTMPROD. SUSAR submission to EVCTM encompasses reporting to the Agency and to all the concerned Member State authorities (including the Medicines Authority) as per the requirements of Clinical Trials Regulation 536/2014. SUSARs do not need to be reported directly to either the Medicines Authority, or the HEC.

The Medicines Authority only requires expedited reporting of reactions arising from clinical trials conducted in Malta and from multi-centre clinical trials which also include Maltese centres.

The requirements for clinical trial sponsors are as follows:

- To keep detailed records of all adverse events and submit them upon request to the Medicines Authority and to the other competent regulatory authorities in whose territory the clinical trial is being conducted.

- Fatal or life-threatening SUSARs as soon as possible but no later than 7 days after the sponsor become aware of the reaction. The sponsor shall submit a completed report within an additional eight days.

• Non-fatal or non-life threatening SUSARs as soon as possible but no later than 15 days after the sponsor become aware of the reaction.

• SUSARs initially considered as non-fatal or non-life threatening but turn out to be fatal or life-threatening must be reported as soon as possible but no later than 7 days after the sponsor become aware of the reaction being fatal or life-threatening.

• SUSARs to IMPs which are identified or come to the attention of the sponsor after the end of the trial have to be reported as well.

The Medicines Authority does **not** require:

- Reporting of ADRs arising from clinical trials conducted outside Malta and which do not involve Maltese centres.
- Reporting of SUSARs arising from foreign clinical trials which involve products authorised in Malta.
- Expedited reporting for reactions which are serious but expected.
- Non serious adverse reactions, whether expected or not.
- Reports considered unrelated to the investigational medicinal product.
- 6 monthly aggregated line listings.

4.8.1 SUSARS ASSOCIATED WITH ACTIVE COMPARATOR OR PLACEBO

Note that active comparators and placebo are IMPs. Therefore, SUSARs associated with comparators follow the same reporting requirements as for the test IMP. Events associated with placebo will usually not satisfy the criteria for a SUSAR and, therefore, neither for expedited reporting. However, where SUSARs are associated with placebos (e.g., reaction due to an excipient or impurity), the sponsor should report such cases.
Only unblinded SUSARs shall be reported in EudraVigilance. Therefore, it is important to have procedures in place to ensure that unblinded information is only accessible to persons who need to be involved in the safety reporting to EudraVigilance, to Data Safety Monitoring Boards (DSMB), or to persons performing ongoing safety evaluations during the clinical trial.

4.8.2 ANNUAL SAFETY REPORT (ASR)

The annual safety report (ASR) is a document provided by the sponsors to the authorities regarding the monitoring and evaluation of the evolving safety profile of the Investigational Medicinal Product (IMP) and the mitigation of potential risks. According to Article 43 of the Clinical Trial Regulation, sponsors shall submit annually a report on the safety of each IMP used in a trial. This obligation starts with the first authorisation of a trial and finalises with the end of the last trial conducted with the IMP. With the information provided via the ASR, the National Competent Authorities (NCAs) are able to both assess each IMP’s safety profile and also enquire further information from the sponsors.

The sponsor shall submit annually via CTIS a report on the safety of the investigational medicinal product used in a CT for which it is the sponsor. ASRs should not be sent directly to the Medicines Authority or the

HEC. The format for an annual safety report (ASR) is according to the ICH guideline E2F on development safety update report. For a detailed description of the ASR consult the 'ICH guideline E2F 'Note for guidance on development safety update reports' [https://www.ema.europa.eu/en/ich-e2f-development-safety-update-report-scientific-guideline] This obligation starts with the authorisation of the first CT under CTR and ends with the end of the last CT conducted by the sponsor with this investigational medicinal product in any MS of the EU/EEA.

In case of a CT involving the use of more than one investigational medicinal product, the sponsor may, if provided for in the protocol, submit a single safety report on all investigational medicinal products used in that CT. A simplified report is acceptable for low intervention CTs and CTs with authorised IMPs

4.9 FEES AND PAYMENTS

Current Fees payable to the Medicines Authority for Clinical Trials are available in Legal Notice 315 of 2006: Marketing Authorisation (Fees) Regulations, 2006 and Pages 194-199 of Legal Notice 427 of 2007.

Current Fees payable to the Health Ethic Committee for Clinical Trials are available in LEGAL NOTICE 29 of 2009: Health Ethics Committee (Fees) Regulations, 2009.

Fees are denoted in Euros.

In the case of full new application or substantial modification affecting Part I and Part II, a single fee consisting of the Medicines Authority fee and the HEC fee, should be paid to the Medicines Authority. The Medicines Authority will then forward the HEC portion of this fee to the HEC.

In the case of partial new application [Part I or Part II only] or substantial modification affecting only Part I or Part II, the fee should be paid to the Medicines Authority or to the HEC, as applicable.

Appropriate proof of payment should always be attached with the application. Payment of the relevant fee should be made at:

Bank Details: HSBC 198, The Strand, Gżira, GŻR 03
Account Name: MEDICINES AUTHORITY
Account Number: 039011176002
IBAN: MT78 MMEB 44392 0000000 39011176002
Swift Code: MMEBMTMT

When effecting the payment the amount should be remitted in full, net of all bank charges.

Whenever a payment is effected in respect of an application which is submitted to the Medicines Authority, the following details need to be submitted to Ms. Analisa Buttigieg on analisa.buttigieg@gov.mt:

1. The name of the company effecting payment
2. The name of the company on behalf of which the payment is effected (when applicable).
3. The amount paid.

4. Date of payment.
5. Type of application.

This information needs to be submitted on the date that the payment is effected.

4.10 CONTACT DETAILS FOR FURTHER INFORMATION

Clinical Trials Unit

Medicines Authority
Sir Temi Żammit Buildings,
Malta Life Sciences Park, San Ġwann
SĠN 3000, Malta
Malta
Europe
Tel: (+00356) 23439000
Email: *info.medicinesauthority@gov.mt*

5. REFERENCES, IMPORTANT AND USEFUL LINKS

1. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance). - Consolidated text. Accessed on *https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02014R0536-20221205&qid=1698402273798*

2. Malta Health Ethics Committee website. Accessed on *https://healthservices.gov.mt/en/appbodies/hec/Pages/hec.aspx*

3. Detailed information on the CTIS system (including sponsor training and registration). Accessed on *https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-training-support*

4. CTIS Questions & Answers. Accessed on *https://euclinicaltrials.eu/guidance-and-q-as/*

5. CTIS live environment workspace. Accessed on *https://euclinicaltrials.eu/*

6. EMA SPOR website. Accessed on *https://spor.ema.europa.eu/sporwi/*

7. Questions and Answers Document – Regulation (EU) 536/2014 [Version 5 (January 2022)]. Accessed on: *https://health.ec.europa.eu/latest-updates/questions-and-answers-document-regulation-eu-5362014-version-5-january-2022-2022-02-01_en*

8. EudraLex - Volume 10 Clinical trials guidelines. *https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en*

9. EudraVigilance: how to register. EMA webpage. Accessible on: https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-how-register

10. ICH guideline E2F 'Note for guidance on development safety update reports'. Accessible on: https://www.ema.europa.eu/en/ich-e2f-development-safety-update-report-scientific-guideline

11. *Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.* Accessed on: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

12. Good Clinical Practice and Requirements for Manufacturing or Import Authorisation of Investigational Medicinal Products (Human Use) Regulations, 2006 (LN 119). Accessed on: *https://legislation.mt/eli/sl/458.47/eng/pdf*

13. Revised CTIS Transparency Rules adopted by the EMA management board. Accessed on *https://www.ema.europa.eu/en/documents/other/revised-ctis-transparency-rules_en.pdf*

Signatures in file