HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Clinical Investigations Carried Out in Ireland

AUT-G0095-5
16 JUNE 2021
This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

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1 SCOPE

The purpose of this guide is to provide an overview of legislation relevant to clinical investigations (CIs) involving medical devices, and guidance on how to submit applications to conduct these CIs in Ireland to the Health Products Regulatory Authority (HPRA).

This guide is primarily targeted at CI sponsors (e.g. manufacturers, academic groups, clinical research organisations) who wish to conduct CIs involving medical devices in Ireland. The information may also prove useful for ethics committees and other stakeholders.

This guidance does not purport to be the definite interpretation of the law and/or regulations and is for guidance purposes only. The relevant legislation relating to medical devices should be consulted in addition to this guide.

2 INTRODUCTION

Regulation (EU) 2017/745 (Referred to as the MDR in the remainder of this guide) is the legislation underpinning the regulation of the safety and marketing of medical devices throughout the European Union. The MDR was published in the Journal of the European Parliament in 2017 and is applicable from 26 May 2021 for elements related to CIs. The MDR has introduced a number of changes with respect to the ethical and scientific review of proposed CIs. This guide aims to help sponsors and other stakeholders prepare to implement the requirements of the MDR.

The MDR describes the operation of an electronic database underpinning a number of functions within the regulation of medical devices in Europe (known as 'EUDAMED'). The European Commission has advised that the modules of EUDAMED that are applicable to CIs will not be functional until 2022. The contingency measures that will be used by the HPRA pending deployment of the CI modules of EUDAMED are detailed throughout this guide.

In general, CIs of investigational medical devices require two types of assessment, from a national competent authority for medical devices and from a relevant research ethics committee prior to beginning the study. For further information on the establishment of a National Research Ethics Committee for medical device research in Ireland related to the MDR, please see the NREC website (www.nrecoffice.ie).

The principles of clinical investigation of medical devices are set out in the European standard ISO 14155:2020. This is an international standard that addresses good clinical practice for the design, conduct, recording and reporting of CIs carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.

3 TYPES OF CLINICAL INVESTIGATIONS

The term 'Clinical Investigation' (CI) is defined in the MDR as any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device. It should be noted that this definition includes the use of non-CE marked and CE marked devices and includes the investigation of devices in healthy volunteers. Specific articles of the MDR go on to detail the expectations for different types of CIs.

3.1 Article 62 – CIs conducted to demonstrate conformity of devices

This article relates to non-CE marked devices being used in CIs for one or more of the purposes specified in Article 62, that is:

- to establish and verify that a device is suitable for its intended purpose and achieves the performance intended by its manufacturer
- to establish and verify the clinical benefits of a device
- to establish and verify the clinical safety of the device and to determine any undesirable side-effects under normal conditions of use and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device

Where a CI is to be conducted to assess a CE marked medical device outside the scope of its intended purpose, it is generally considered in the same way as a CI of a non-CE marked medical device.

Sponsors of CIs being undertaken for the purposes listed above, for devices of all risk classes (Class I to Class III), should apply to the HPRA for approval before conducting the CI in Ireland. The requirements and expectations for these CIs are detailed in Articles 62 to 81 of the MDR, along with Annex XV.

3.2 Article 74 – CI regarding devices bearing the CE marking

Where a CE marked device is used within its intended purpose in a CI, the MDR requires that sponsors assess whether subjects will be submitted to additional procedures that are deemed invasive or burdensome. Where this is the case, the sponsor will be expected to notify the HPRA of their intention to undertake that CI and will be expected to include, with the notification, the documentation referenced in Article 74 of the MDR.

It should also be noted that studies conducted under Article 74 of the MDR will require an ethical review by a relevant research ethics committee before they can be commenced.

3.3 Article 82 – Requirements regarding other CIs

When a CI is not performed for any of the purposes listed in Article 62 (summarised above), the CI will still need to comply with specific elements of the provisions of Article 62, including in

relation to the legal status of the sponsor and in relation to the protections offered to the subjects in the CI.

In addition, for studies carried out in Ireland under this part of the MDR, specific national provisions apply. These provisions are set out in Regulation 14 of the Irish Medical Devices Regulations 2021 (S.I. 261 of 2021) and sponsors should consult the relevant legislation to ensure they meet all relevant provisions. In brief, these provisions include:

- Sponsors must notify the HPRA in writing at least 30 days prior to commencement of the study.
- Articles 69 and 76 of the MDR will apply to these clinical investigations.
- Adverse events or vigilance reports (as relevant) must be reported in accordance with the requirements set out in the MDR.

The HPRA may also have additional requirements on a case by case basis following notification of the clinical investigation.

Sponsors intending to notify the HPRA of clinical investigations under Article 82 of the EU MDR are encouraged to engage with the Medical Devices department for further information on the notification process.

3.4 Annex XVI devices

The MDR introduces regulatory requirements for specific devices without an intended medical purpose, with the devices listed in Annex XVI of the Regulation. The MDR does foresee CIs with these devices, where necessary as part of their clinical evaluation. CIs for these devices conducted in Ireland will be assessed in a process similar to devices with an intended medical purpose.

4 MAKING AN APPLICATION

4.1 Clinical investigations of non-CE marked medical devices

An application for a CI consists of the following:

- a completed 'Application for a clinical investigation of non-CE marked medical devices under MDR' form available at www.hpra.ie
- any required documentation as per Annex XV of the MDR
- the relevant fee (see the 'Guide to Fees for Human Products')

Step-by-step information on the procedure for submitting an application or notification to the HPRA is available on the clinical investigations webpage.

Prior to submission of an application, the HPRA strongly encourages manufacturers or sponsors to arrange a pre-submission meeting with the HPRA's clinical investigation review team to discuss the proposed CI. Further information on these meetings is available on the HPRA clinical investigations webpage.

4.2 Changes or modifications to the clinical investigation

Modifications to CIs that have been previously approved by the HPRA should be notified in line with Article 75 of the MDR. Until the relevant functionality of the EUDAMED system is established, these notifications should be made to the HPRA via CESP and an accompanying email to devices@hpra.ie, following the steps as detailed on the HPRA clinical investigations webpage.

As highlighted in ISO 14155:2020, 'Documentation of changes [to IB, CIP, CRFs, informed consent form and other subject information or other clinical investigation documents such as instructions for use] shall include a description of the changes, justification of the changes and their potential impact on the performance, effectiveness, safety or other endpoints, and identification of the affected documents.' The MDR requires that changes to the relevant documentation are clearly identifiable. In order that the changes are clearly identifiable, the HPRA expects that, in addition to the relevant application form, any substantial modifications are notified in the format provided in Appendix 2 of this guide.

Article 75 of the MDR does not describe how sponsors or authorities will deal with non-substantial modifications. Once EUDAMED is available, sponsors are expected to keep the information in the database up to date in accordance with Article 70(2) of the MDR. In the absence of EUDAMED, non-substantial modifications will require an application to the HPRA prior to implementation.

It should be noted that a review and positive opinion, relating to any proposed modifications, may also be required from the relevant research ethics committee prior to their implementation.

Where the proposed modifications may have major implications on the risk/benefit considerations for the CI overall, the HPRA may request the submission of a new CI application.

4.3 Clinical investigations of CE marked medical devices

When a sponsor intends to undertake a CI using a CE marked medical devices within its intended purpose, notification of this CI to the HPRA may be required in certain circumstances. Notification to the HPRA is required where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome.

When notification to the HPRA is required, the sponsor should complete the relevant form (Notification of a clinical investigation under Article 74 of the MDR), and submit this along with the relevant documents via CESP. The sponsor should also send an email to devices@hpra.ie to advise that a notification has been submitted via CESP, along with the reference number provided by the CESP system for a successful submission.

Following notification to the HPRA, and subject to any relevant requirements for research ethics committee approval at the relevant sites, the sponsor may commence the CI after 30 days.

4.4 Clinical investigations under Article 82

Sponsors intending to notify the HPRA of studies carried out under Article 82 of the MDR should complete the form 'Notification of a clinical investigation under Article 82', available on the HPRA website, and submit this via CESP, along with any relevant documentation. The sponsor should also email devices@hpra.ie to advise that a notification has been submitted via CESP and give the reference number provided by the CESP system for a successful submission.

5 PROCESS FOR HPRA REVIEW OF CLINICAL INVESTIGATIONS OF NON-CE MARKED MEDICAL DEVICES

On receipt of an application to undertake a CI, the application is validated in order to check that all the required documentation is present and that the proposed CI falls within the scope of the MDR.

At that time, a HPRA reference number is assigned to the application and this should be quoted in all future correspondence with the HPRA. All CIs undertaken in Europe should also be assigned a CIV ID from the Eudamed 2 system. If you have already been issued with a CIV ID for the same investigation being conducted in another Member State, please provide this to the HPRA on the application form.

Once validated, the application then undergoes a preliminary review to determine if external experts are required to assist with the review. If external experts are used, they will have signed a confidentiality agreement with the HPRA that incorporates a declaration of conflicts of interest. All external experts will be required to confirm destruction or return all submitted documentation issued to the HPRA post review.

The HPRA will assess and provide an outcome of its assessment within 45 calendar days of validation of an application. Where the HPRA needs to consult with an expert during the period of assessment, an additional 20 calendar days is added to the time available for assessment by the HPRA. During the assessment period, the HPRA may request additional information from the sponsor of the CI. Any time taken for the sponsor to provide this additional information is not included within the assessment period described above. This process applies to all risk classes of medical devices, i.e. Class I to III.

Where a response is not provided to the issues raised by the HPRA within the timeframe this may result in rejection or refusal of the application due to incomplete data being available to support the application.

6 REFUSAL OF AUTHORISATION OF A CLINICAL INVESTIGATION

The HPRA may refuse to authorise the CI if, after consideration of all the evidence provided by a manufacturer or sponsor, the grounds for authorisation of the CI are not met or there are grounds for refusal. The reasons for a refusal to authorise a CI will be provided in written form to the sponsor.

Following receipt of the notification of refusal to authorise a CI, the applicant has the right to appeal the decision as per the procedure detailed in the 'Guide to Refusals and Appeals', available at www.hpra.ie.

7 REPORTING OF ADVERSE EVENTS

Safety reporting of adverse events in CIs should be made to the HPRA in line with the guidance issued by the MDCG (MDCG 2020 -10/1 Guidance on safety reporting in clinical investigations). Serious adverse events and device deficiencies are defined in the MDR and the following events are considered reportable in accordance with MDR Article 80(2):

a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b).

MDCG 2020 10/1 provides additional guidance regarding the reporting of serious adverse events during a CI including timelines for reporting to national competent authorities. Until such a time as the CI modules of EUDAMED are fully functional, the HPRA expects sponsors to submit relevant event reports to the HPRA to devices@hpra.ie using the template provided by the MDCG, along with the reference number assigned to the CI.

It should be noted that, in accordance with the Irish Medical Devices Regulations 2021 (S.I. 261 of 2021), adverse events relating to clinical investigations of non CE-marked medical devices meeting the definition in Article 82 of the MDR will need to be reported to the HPRA.

8 END OF CLINICAL INVESTIGATION IN IRELAND

The HPRA expects that sponsors undertaking a CI in Ireland will submit a notification of the end of the CI to the HPRA within 15 days of the end of the CI.

This notification should be followed by the submission of a report to the HPRA on the CI, within one year of the end of the CI. The requirements for this report can be found in Annex XV of the

MDR. Where a CI has been terminated early or where a temporary halt has occurred, the CI report should be submitted to the HPRA within three months.

Until such a time as the CI modules of EUDAMED are fully functional, the HPRA expects sponsors to submit this notification and subsequent report to devices@hpra.ie along with the reference number assigned to the CI.

9 ADMINISTRATIVE DETAILS

This guide and associated documents can be found under the publications and forms section of www.hpra.ie.

Alternatively, they can be obtained from the HPRA directly as follows:
Telephone: +353-1-6764971
Email: devices@hpra.ie

The HPRA encourages communication with the medical device sector. Should you have specific queries please address them to the Medical Devices Department of the HPRA who will endeavour to be of assistance.

APPENDIX 1 REFERENCES

1 Regulation (EU) 2017/745 of the European Parliament and of the Council on Medical devices

2 ISO Standard 14155: 2020 Clinical investigation of Medical devices for human subjects – Good clinical practice

3 MDCG 2020 10/1 Guidance on safety reporting in clinical investigations

APPENDIX 2 TEMPLATE FOR NOTIFYING MODIFICATIONS

Format of document identifying proposed modifications to approved CI:

Document and location reference	Original text	Amended text	Rationale
e.g. CIP001 Page 2 Section 1.11	The study will be performed at the following sites: Hospital A Hospital B	The study will be performed at the following sites: Hospital A Hospital B Hospital C	An additional investigational site will be added due to….