HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide for
Manufacturers and Sponsors on Clinical Investigations Carried Out 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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1 SCOPE

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

This guide is primarily targeted at clinical investigation sponsors (e.g. manufacturers, academic groups, clinical research organisations) who wish to conduct clinical investigations 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

A series of three Directives regulate the safety and marketing of medical devices throughout the European Community. They are as follows:

1 Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC and related S.I. No. 253* of 1994.

This Directive covers all medical devices that meet the definition of an active implantable medical device per the above Directive and S.I. This includes medical devices such as pacemakers, implantable defibrillators, implantable infusion pumps, cochlear implants and implantable neuromuscular stimulators. This Directive also includes implanted passive parts of active devices like pacemaker leads and adaptors, and external parts that are an essential part of the system.

2 Medical Devices Directive (MDD) 93/42/EEC* and related S.I. No. 252* of 1994.

This Directive covers all devices that meet the definition of a medical device per the above Directive and S.I. This Directive covers a wide range of medical devices including bandages, orthopaedic implants and radiotherapy equipment. This Directive also includes devices incorporating as an integral part a substance which, if used separately, may be considered a medicinal product or a human blood derivative.

3 In-vitro Diagnostic Medical Devices Directive 98/79/EEC concerning (IVD's) and related S.I. No. 304 of 2001.

This Directive covers any medical device that meets the definition of an in vitro diagnostic medical device per the above Directive and S.I.

The Directives are intended to ensure the safety and performance of medical devices and to prohibit the marketing of devices that may compromise the health and safety of patients and users.

The above Directives list the essential requirements to be met before a device can be placed on the market or put into service. The AIMD and MDD specify the requirements for performing clinical evaluations to demonstrate conformance with these essential requirements.

There is no legislation relating to clinical investigations for IVDs. Rather IVDs may require a performance evaluation prior to CE marking and release onto the market. Legislation relating to performance evaluation is contained in the above-referenced IVD Directive.

The principles of clinical investigation of medical devices, excluding IVDs, are set out in the European standard ISO 14155:2011. This is a harmonised standard which addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. This harmonised standard provides a means for getting presumption of conformity to the part of the essential requirements of MDD and AIMD that refers to clinical investigations.

*as amended

3 CLINICAL EVALUATIONS

In order to obtain a CE mark for a device, a manufacturer must demonstrate the basic safety and performance of the device and conformance of the device with the essential requirements described in Annex I of the relevant Directive. This demonstration of conformance must include an evaluation of this data, referred to as 'clinical evaluation', should follow one of the following procedures:

a) a critical evaluation of the relevant scientific literature currently available relating to the device
b) a critical evaluation of the results of all clinical investigations generated for the device
c) a critical evaluation of the combined clinical data provided in a) and b) above

In the case of implantable and Class III medical devices the Directives, as amended by Directive 2007/47/EEC, state that clinical investigations shall be performed unless it is duly justified to rely on existing clinical data alone. Justification for not conducting a clinical investigation for devices of this type should be clearly documented and substantiated with relevant supporting data which demonstrates conformance with the relevant essential requirements and addresses issues such as equivalence. The clinical evaluation and its documentation must be actively updated

with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.

Clinical evaluation should be conducted in accordance with European guidance documents (e.g. MEDDEV 2.7/1) and, where appropriate, other relevant international documents such as those published by the International Medical Device Regulators Forum (IMDRF). In circumstances where a clinical evaluation for a class III or implantable medical device does not include a specific clinical investigation of that device in circumstances where sufficient data is available from appropriate and equivalent devices, the manufacturer should conduct post-market clinical follow up studies of the device in accordance with the relevant European guidance.

4 TYPES OF CLINICAL INVESTIGATIONS

The term clinical investigation is defined in ISO Standard 14155 as '…any designed and planned systematic study in human subjects undertaken to verify the safety and/or performance of a specific device'.

Different types of medical device investigations are conducted in healthcare settings in Ireland but only certain types of these clinical investigations require notification and review by the HPRA prior to commencement.

4.1 Clinical investigations requiring notification/no objection

Clinical investigations that are likely to require notification and review by the HPRA prior to commencement include:

- New devices: when a novel device is being used in human subjects for the first time where the device components, features and the methods of action are previously unknown.
- Modification of an existing device: if a device is modified significantly such that the safety and/or clinical performance may be affected.
- Device containing untested materials: if a proposed device contains materials which have not previously been tested in contact with human subjects.
- Device materials used in a different location or for a different duration: when existing materials are used and come in contact with new body locations or are used for a significantly longer duration.
- Device proposed for a new function: where a device is being used for a new function outside of the manufacturers' indications for use/intended purpose.

4.2 Clinical research versus clinical investigation and 'off-label' investigations

Some medical device clinical investigations that are conducted within healthcare settings do not require notification or review by the HPRA.

Device investigations that are proposed, designed and sponsored by clinical investigators rather than medical device manufacturers, solely for the purposes of clinical or academic research with no commercial intent, may not require review by the HPRA prior to commencement. In such instances, investigational devices should be used within acceptable professional and ethical boundaries and for the purposes of research only. This also applies to cases when:

- device investigations are conducted without the financial support of the manufacturer
- when it is not planned to use the data generated as part of an application for conformity assessment
- when there is no intent to seek commercial gain on the basis of the clinical data that are generated

When a medical device that bears the CE mark is used outside of its intended use and indications, it is considered to be the same as a non-CE marked device, i.e. subject to clinical investigation application. Some investigations of this type however that are conducted in healthcare settings on the initiative of healthcare professionals or academics may not require application to the HPRA. While such 'off-label' clinical studies may in fact be seeking to verify emerging clinical practice it is important that the sponsor and investigational centre are aware of any safety, performance and legal implications. Full responsibility for 'off-label' use may transfer from the device manufacturer to the investigator and investigational centre. Clinical investigators involved in such studies should ensure that they have access to relevant data from the device manufacturer to indicate if the device can be used safely in this 'off-label' manner. The device manufacturer may not have relevant pre-clinical data or may, in fact, have data which does not support the safe use of the device in an off-label fashion.

In such cases where the sponsor is finding it difficult to determine whether a submission for review by the HPRA is necessary, the HPRA is happy to discuss the planned investigation(s) to determine if an HPRA review process would be required through the contact details provide in this document.

5 CLINICAL INVESTIGATION REQUIREMENTS

Where a clinical investigation is required, the investigation must:

- be performed on the basis of an appropriate plan with well-defined aims and objectives
- be performed in circumstances similar to the intended use of the device, i.e. consideration given to patient populations, user groups, training and facilities
- use procedures that are appropriate to the device under examination
- include sufficient devices and human subjects to reflect the aims of the investigation taking into account the potential risk of the device
- examine appropriate features involving safety and performance and their effects on patients so that the risk/benefit balance can be satisfactorily addressed

- fully record and report to the HPRA all adverse device events and all serious adverse events and report as per MEDDEV 2.7/3
- be performed under the responsibility of one or more medical practitioners or other appropriately qualified personnel
- be conducted in line with any conditions or obligations outlined in HPRA correspondence/approvals
- include a final report to be submitted to the HPRA within three months of completion, signed by the principal coordinating investigator and each national investigator containing a critical evaluation of all the data collected, including assessment of serious adverse events during the investigation with appropriate comments and conclusions

The legal requirements and ethical considerations relating to clinical investigations are set out in Regulation 10, schedules 6 and 7 of S.I. No. 253of 1994 as amended and in Regulation 16, and schedules 8 and 10 of the S.I. No. 252 of 1994 as amended. Relevant harmonised standards, such as European standard EN ISO 14155:2011 and agreed European and international guidance (e.g. MEDDEV) should be used as a reference when planning a clinical investigation for submission to the HPRA.

For all clinical investigations falling within the scope of the AIMD and MDD, a relevant local ethics committee opinion is required. In the case of multi-centre clinical investigations, opinions must be obtained from each participating centre. Only those centres that have provided the local ethics committee opinion may commence clinical investigation when no objection has been raised by the HPRA.

The number of subjects to be recruited in a clinical investigation should be based on the objectives, investigational design and investigational phase and be supported by relevant justifications, e.g. statistical validity and clinical development plans. For pivotal clinical investigations, the number of devices to be used in a clinical investigation must be sufficient to demonstrate performance satisfactorily and to reveal significant risks to patients' health and safety.

The manufacturer or the authorised representative must prepare a written report on completion of the clinical investigation. This report must be submitted to the HPRA within three months of completion of the investigation, unless otherwise agreed in writing.

5.1 Labelling of devices for clinical investigation

Devices intended for clinical investigation should be clearly identified as being exclusively for clinical investigation, e.g. bear a label with the wording 'exclusively for clinical investigation'. Manufacturers should draw this requirement to the attention of all clinical investigators and investigators should ensure that the meaning of this wording is clearly understood by all staff using or coming into contact with the devices under investigation. The devices should be segregated, where possible, from any similar devices in use that are not part of the clinical investigation.

Where a clinical investigation involves non-CE marked medical devices, the non-CE marked devices under investigation must not bear the CE mark on their labels.

6 MAKING AN APPLICATION

An application for a clinical investigation consists of the following:

- a completed 'Application for Clinical Investigations on Medical Devices' or 'Application for Amendments to Clinical Investigations on Medical Devices' form available at www.hpra.ie
- any required documentation
- the relevant fee (see the 'Guide to Fees for Human Products')

The HPRA will assess and provide an outcome of its assessment within 60 days of validation of an application. This process applies to all risk classes of medical devices, i.e. class I to III.

Prior to submission of an application the HPRA encourages manufacturers or sponsors to arrange a pre-submission meeting with the HPRA's clinical investigation review team to discuss the proposed clinical investigation.

Ethics committee review can be conducted in parallel with review by the HPRA, i.e. application can be made to the HPRA once an application has been sent to the relevant ethics committee. The HPRA must receive the final opinion of the ethics committee before it completes its review.

All applications (including the supporting data) must be in English. The HPRA strongly recommend electronic submission of clinical investigation applications by email or on CD/DVD. Electronic submissions are acceptable in Word or pdf format.
The following recommendations apply for electronic submissions:

- A 'table of contents' should be included as a separate file, identifying the different sections of the clinical investigation submission.
- A separate file should be created for each of the main sections identified in the 'table of contents' and should be clearly identified in the file name.
- File names should be consistent and easily correlated to section numbering and titles in the table of contents', e.g. 'Section 2_RiskAssessment'.
- Attachments that are referenced in the application documents submitted as separate files should be clearly identified in the file name, e.g. 'Section2_Risk Assessment_Attachment1'.
- All applications must contain a statement of compliance to the essential requirements applicable to the aspects of the device to be investigated.
- PDF files should be submitted in Optical Character Recognition (OCR) format.

The following recommendations apply for electronic submissions by email:

- Due to mailbox limitations, emails should be less than 10Mb in size. Where the application size is greater than 10Mb, multiple emails should be submitted.

- Email applications should be accompanied by a cover email, without attachments, stating the intention to submit the clinical application to the HPRA and should include the following information:
  - applicant's name
  - name of medical device
  - investigation name and sponsor's reference number (if available)
  - number of emails per application
- Each email submitted should be clearly identified in the subject line, e.g. '<Clinical investigation name>, <Device name>, Email <x of y>'.

The following recommendations apply for electronic submissions by CD/DVD:
- Where more than one CD is required, please use a DVD.
- Each CD or DVD submitted in electronic format must include the following label information, clearly presented and printed on the media:
  - applicant's name
  - name of medical device
  - investigation name and sponsor's reference number (if available)
- A cover letter should be included stating the intention to submit the clinical application to the HPRA and should include the following information:
  - applicant's name
  - name of medical device
  - investigation name and sponsor's reference number (if available)

7 PROCESS FOR REVIEW AT THE HPRA

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

At that time a reference number is assigned to the application that should be quoted on all future correspondence with the HPRA.

Once validated, the clinical investigation 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 conflict of interest. All external experts will be required to confirm destruction or return all submitted documentation issued to the HPRA post review. A detailed review of the application is completed by day 30, and if further information is required by the HPRA, the manufacturer is contacted to provide this data. A response should be submitted by the manufacturer to the HPRA by day 44. This additional data is then reviewed by the HPRA expert team by day 49 and a final report is prepared. An internal meeting is convened by day 55 with all relevant experts involved in the assessment of the application. If after consideration of all the data provided by the manufacturer the HPRA considers that there are no grounds relating the health and safety

whereby the clinical investigation should not proceed, the HPRA will notify the applicant of the decision by day 60.

If the HPRA in discharging its function is of the opinion that the device in question should not be made available for the purposes of clinical investigation until such time as queries raised are satisfactorily replied to, the HPRA may suspend the 60 day clock on the basis of a concern for the health and safety of patients, users or others of the device. When a response has been received from the manufacturer or the authorised representative, the clock will restart and continue.

It must be pointed out that if a response is not provided to the issues raised by the HPRA within the timeframe it may result in rejection of the application due to incomplete data being available to support the application.

The manufacturer or the authorised representative must prepare a written report on completion of the clinical investigation. This report must be kept at the disposal of the HPRA. The HPRA may request a copy of the final written report of a clinical investigation. It is likely that a copy would be requested under certain circumstances, e.g. where a serious adverse incident has occurred with a CE marked device which has undergone clinical investigation authorised by the HPRA.

8 OBJECTION TO A CLINICAL INVESTIGATION

If, after consideration of all the evidence provided by a manufacturer or sponsor that, there are grounds relating to health and safety whereby the clinical investigation should not proceed, the HPRA will notify the applicant of the decision. Reasons for the objection will be clearly stated in the letter of objection.

Unjustifiable risks to public health and safety may exist, e.g.:

- where there are reasonable grounds to suspect that a device does not satisfy relevant essential requirements
- where there are reasonable grounds to suspect that the clinical investigation is not subject to controls equivalent to the requirements of the relevant European standard (EN ISO 14155:2011)
- when it is deemed that the proposed clinical investigation that has an unfavourable benefit risk profile, where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical investigation to be made
- where the manufacturer or sponsor has delivered documentation necessary for complete assessment of the application so late that insufficient time remains to complete the assessment

Following receipt of the notification of objection to a clinical investigation, 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.

9 CHANGES OR MODIFICATIONS IN PROTOCOL

All changes in protocol whether relating to the device, aspects of the clinical investigation plan, investigator or investigation institutions must be notified to the Competent Authority and should not be implemented until a letter of agreement has been obtained from the Competent Authority.

Technical amendments to the existing protocol will require specific application with further supporting documentation for review by the HPRA. Such applications should be accompanied by the relevant fee.

The Competent Authority retains the right to request a new clinical investigation notification if the modification to the protocol is thought to increase the risk to either the patient or the user, or if the Competent Authority considers that the changes proposed constitute a new investigation.

10 REPORTING OF ADVERSE EVENTS

Any serious adverse event (SAE) involving a device under clinical investigation within the scope of the Directives should be reported to the HPRA as required by the Medical Devices Regulations 1994 S.I. No. 252 of 1994 as amended and S.I. No. 253 of 1994 as amended and in accordance with MEDDEV 2.7/3.

Serious adverse events that should be reported include adverse events that led to:
- death or a serious deterioration in health
- prolonged hospitalisation, additional surgery or medical intervention
- a life-threatening illness or injury

Reportable events also include device deficiencies that might have led to a serious adverse event if suitable action had not been taken or intervention had not been made.

MEDDEV 2.7/3 provides additional guidance regarding the reporting of serious adverse events during a clinical investigation including timelines for reporting to national competent authorities. The HPRA is happy to accept summary tabulations of serious adverse events as outlined in this document, however the HPRA may request more specific information on specific serious adverse events if deemed necessary.

11 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:

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

Telephone: +353-1-6764971
Fax: +353-1-6767836
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.

Communication can be made by telephone, fax, email or by post to the above address.

APPENDIX 1 REFERENCES

1 Directive 90/385/EEC concerning active implantable medical devices

2 Directive 93/42/EEC concerning medical devices

3 Directive 98/79/EEC concerning in vitro diagnostic medical devices

4 Statutory Instrument 252 of 1994, European Communities (Medical Devices) Regulations, 1994

5 Statutory Instrument 253 of 1994, European Communities (Active Implantable Medical Devices) Regulations, 1994

6 Statutory Instrument 304 of 2001, European Communities (in vitro Diagnostic Medical Devices) Regulations, 2001

7 ISO Standard 14155'Clinical investigation of Medical devices for human subjects – Good clinical practice'

8 MEDDEV 2.7/1 Clinical evaluation: Guide for manufacturers and notified bodies

9 MEDDEV 2.7/3 Clinical investigations: serious adverse event reporting

10 MEDDEV 2.7/4 Guidelines on Clinical Investigations: a guide for manufacturers and notified bodies

11 HPRA 'Guide for Ethics Committees on Clinical Investigations for Medical Devices'