Guide for
Ethics Committees on Clinical Investigation of Medical Devices
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1 INTRODUCTION

The purpose of this guide is to provide an overview of the legislation that is relevant to clinical investigations involving medical devices that are conducted in Ireland, and to highlight the role of the Competent Authority (e.g. the Health Products Regulatory Authority) in the review process. This document is not intended to act as guidance on ethical issues or decision-making relating to device investigations.

This guide is primarily targeted at research Ethics Committees in Ireland who review applications to conduct clinical investigations involving medical devices. The information may also prove useful for clinical investigators and other stakeholders.

This guide does not purport to be the definite interpretation of the law and / or regulations and is for guidance purposes only. Readers are therefore advised to consult the relevant legislation relating to medical devices.

Information and assistance can be obtained from the Health Products Regulatory Authority (HPRA). The relevant contact details are included in section 15 of this document.

2 BACKGROUND, SCOPE AND CONSULTATION PROCESS

During the development of this document, the HPRA met with a variety of Irish Ethics Committees in an effort to identify experience with device investigations, key issues and concerns relating to medical device investigations. This consultation process suggested the following:

- In general, Irish Ethics Committees have, to date, had limited exposure to clinical investigations involving medical devices. However, it is likely that this exposure will increase, as in recent years, the number of and the interest in medical device investigations in Ireland has increased. This is partly due to the stronger focus in this area by all the stakeholders in the process, including industry, regulators, academics and clinicians. In addition, a revision to the Medical Devices Directive which came into effect in March 2010 increases the emphasis on, and need for, clinical investigations of medical devices.

- The Medical Devices Directive (93/42/EEC and S.I. 252 of 1994) contains all specific legislation relating to general medical device investigations. Further reference to devices legislation is contained in section 4 and appendix B of this document. A commonly held perception is that the Clinical Trials Directive (2001/20/EC) is applicable to clinical investigations which involve medical devices. However, the Clinical Trial Directive applies only to trials involving medicinal products (this may include some of the drug-device combination products).
- There is uncertainty about the type of medical device investigations that require review by the HPRA prior to commencement. Not all device investigations require review by the HPRA, details are provided in section 5 of this document.

- Clinical investigations involving medical devices that already carry a CE mark often do not require review by the HPRA. However, when devices are used outside of their existing indications for use or outside the terms of their CE marking e.g. ‘off-label’ investigations, clinical investigations may require review and approval by the HPRA. Clinical investigators who act as sponsor for ‘off-label’ investigations acquire responsibility for all relevant regulatory obligations.

- Drug-device combination products were frequently raised for discussion in relation to their classification and the review of these investigational products. Further information on these products is contained in section 10 of this document.

- The review of the technical and design aspects of medical devices used in investigations can cause concern for Ethics Committees. Clinical investigation documentation is reviewed, when applicable by the HPRA, from technical, clinical and regulatory perspectives. Therefore, technical and design aspects of the device are included in the HPRA review.

3 WHAT IS A MEDICAL DEVICE?

There are many different types of medical devices available across the European Union. All medical devices which are placed on the EU market must carry a CE mark unless this device has been approved to be made available for clinical investigation only.

Clinical investigations may involve one of two types of medical device i.e. a general medical device or an active implantable medical device, e.g. implantable infusion pump. Medical devices are classified, largely on the basis of risk, into four classes i.e. class I, class IIa, class IIb and class III. Risk increases from class I to class III and classification is proposed on the basis of the intended use of the device, the degree of invasiveness of the device, the body location in which the device is used and experience from the use of similar devices.

In-vitro diagnostic devices are a separate category of devices and include laboratory assays, reagents, glucometers and diagnostic test kits.

A medical device is defined in Article 1.2 of the Medical Devices Directive (93/42/EEC) as “…any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation or compensation of an injury or handicap,
- investigation, replacement or monitoring of the anatomy or a physiological process,
- control of conception."

4 CLINICAL INVESTIGATION

The term clinical investigation is defined in ISO Standard 14155, ‘Clinical Investigations of Medical Devices for Human Subjects’, as “…any designed and planned systematic study in human subjects undertaken to verify the safety and/or performance of a specific device.”

The term ‘clinical investigation’ rather than clinical trial is generally used when referring to device-related research.

The majority of clinical investigations that require review by the HPRA involve non-CE marked medical devices and are submitted by medical device manufacturers. In these instances the manufacturer is proposing to conduct an investigation to gather the necessary clinical data to demonstrate the basic safety and performance of their device and the conformance of the device with the Essential Requirements described in Annex I of the Medical Devices Directive (93/42/EEC). This is an integral step in the manufacturer obtaining a CE mark for their medical device which allows them to freely market it throughout the EU.

When a clinical investigation is completed, the manufacturer submits the data gathered during the clinical investigation along with relevant pre-clinical, technical and design data to a Notified Body. If the Notified Body is satisfied, after review of data submitted, that the device is in conformance with the Essential Requirements of the Directive they may award the device a CE mark. Clinical investigation/data is not always provided in support of a CE mark and its necessity can depend on the class of the device (i.e. class I-III). These concepts are further elaborated in Appendix A.

5 OVERVIEW OF RELEVANT LEGISLATION


A complete list of relevant legislation, for reference, is contained in Appendix B.

Legislation relating to clinical investigations which involve medical devices is contained in the applicable Medical Device Directive (93/42/EEC) or the Active Implantable Medical Device Directive (90/385/EEC). Some excerpts from 93/42/EEC are contained in Appendix C of this document.
There is no legislation relating to clinical investigations in the *In-vitro* Diagnostic (IVD) Devices Directive (98/79/EC). 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 Directive.

These Directives:

- Specify ‘essential requirements’ which must be met before any device can be placed on the market or put into service,

- Introduce controls covering the safety, performance, specification, design, manufacture and packaging of devices,

- Specify requirements for assessment of clinical investigation protocols, and the evaluation of any adverse incidents that occur,

- Introduce a system of classifying devices, and apply a level of control which is matched to the degree of risk inherent in the device,

- Empower a Competent Authority to identify and designate ‘Notified Bodies’ who check and verify that devices meet the relevant essential requirements. Definitions of Competent Authority and Notified Body are available in Appendix A,

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

NB: The general Medical Devices Directive (93/42/EEC) has been significantly amended by a recently published Amendment 2007/47/EC. This has significant changes in relation to the requirements for clinical investigations. A transitional period is defined within this Amendment which is not mandatory until 2010.

### 6 CLINICAL INVESTIGATIONS REQUIRING NOTIFICATION/NO OBJECTION

Only certain types of clinical investigation involving medical devices require notification and review by the HPRA prior to commencement. In general, clinical investigations which require review by the HPRA are proposed by commercial sponsors e.g. medical device manufacturers who are introducing a new non-CE marked medical device to the market. As described in section 4, the aim of conducting a clinical investigation, in this instance, is to gather clinical data to support the safety and basic performance of the device and demonstrate conformance with the Essential Requirements of the relevant device Directive. This is an integral step in the process of obtaining a CE mark.
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 manufacturer’s indications for use/intended purpose.

Clinical investigations of medical devices which are already CE marked often do not require notification and review by the HPRA provided these investigations are conducted within the device’s existing intended purpose and indications for use. However, if the investigation is proposed to gather data to support an extension of the current indications for use then review and approval may be required prior to commencement.

Clinical investigation applications may be submitted to the HPRA for review in parallel to the application made to the relevant ethics committee. The full opinion of the ethics committee must be submitted to the HPRA prior to the HPRA finalising its review and granting an opinion on the application. A favourable final opinion from the relevant ethics committee and a letter of no objection from the HPRA are required prior to the commencement of any such investigation.

For clinical investigations with multiple centres in Ireland, an opinion is required from each relevant ethics committee involved. The ethics committee responsible for providing an opinion for a specific site is subject to institutional and/or national ethics policy. Currently, several ethics committees can review applications on behalf of multiple clinical sites. When an opinion is required from several ethics committee for a specific investigation the application can be made to the HPRA upon submission of an application to the first ethics committee. Subsequently, further centres can be added with the further additional ethics committee opinions by administrative amendment.
7 DETAIL OF REVIEW PROCESS AT THE HEALTH PRODUCTS REGULATORY AUTHORITY

Clinical investigations involving medical devices undergo review by the HPRA over a 60 calendar-day period as defined in the Irish and EU legislation. The documentation is reviewed from regulatory, technical and clinical perspectives by a panel of reviewers within the Human Products Authorisation and Registration Department, whose personnel include individuals with industrial/manufacturing, medical, engineering, scientific, pharmaceutical and research backgrounds. Advice may be sought from individuals outside the HPRA who have expertise relating to the clinical use of the specific device type. External technical expertise may also be sought for certain device types.

Documentation typically reviewed by the HPRA includes: the device risk analysis, design documentation, materials documentation, cytotoxicity/biocompatibility data, sterilisation, pre-clinical data, existing clinical data and the clinical investigation protocol, patient information sheets/consent forms and the investigator’s brochure. Further documentation may be requested by the HPRA during the course of the review process.

After an initial 30-day review by the internal and external panel of reviewers, questions and issues relating to the investigation review may be addressed to the investigation sponsor e.g. device manufacturer. The manufacturer must provide satisfactory responses to these issues within an allotted timeframe, typically 14 days.

By day 60 of the review process the final opinion of the review panel is referred to the Management Committee of the HPRA for decision. The HPRA then communicates the decision to the sponsor. In most cases a ‘Letter of No Objection’ is issued and the clinical investigation may proceed. If an ‘Objection’ to an investigation is raised by the HPRA, the reasons for the objection are conveyed in detail to the sponsor.
8 CLINICAL RESEARCH VERSUS CLINICAL INVESTIGATION AND ‘OFF-LABEL’ INVESTIGATION

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

It is important to draw a distinction between device investigations that are conducted purely for commercial reasons and device investigations that are conducted as part of academic or clinical research. Device investigations that are proposed, designed and sponsored by clinical investigators rather than 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 applies to device investigations which are conducted without the direct financial support of the manufacturer and when there is no intent to seek commercial gain on the basis of the clinical data that are generated.

‘Off-label’ device investigations relate to circumstances where a device is being used outside its existing intended purpose or indications for use for investigational purposes. Use of the device in this manner may, since the market release of the device, have become an established or standard clinical practice. This type of clinical investigation is often led directly by clinicians and has no commercial basis and therefore may not require review by the HPRA prior to commencement.

Alternatively, manufacturers may directly or indirectly sponsor these off-label studies with a view to extending their devices current indications for use. In these instances it is likely that a full review, including all relevant data, will be required.

The off-label use of devices, whether as part of a clinical investigation or not, should be undertaken with caution. Clinical investigators should request 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 do not support the safe use of the device in an off-label fashion.

NB: Investigators and investigational centres should remember that full responsibility for ‘off-label’ use is carried by the investigator and investigational centre.

The distinction between investigations which require review by the HPRA and these which do not can sometimes be difficult to determine. The HPRA is happy to discuss specific investigations to determine if an HPRA review process would be required.
9 PRE-CLINICAL TESTING

Before medical devices are used in human subjects in clinical investigations they commonly undergo various types of pre-clinical testing. This pre-clinical testing should be designed to demonstrate the basic safety and efficacy of the device and uncover any major risks associated with the device prior to any exposure to human subjects. It should be conducted in line with relevant international standards for the device type and should include sufficient devices with sufficient duration of testing. A list of harmonised standards relevant to medical devices can be downloaded from the European Commission’s website.

Pre-clinical testing of medical devices may be designed to demonstrate structural or physical properties of the device through various types of in-vitro investigations such as: simulated use/bench testing investigation, computer modelling, cadaveric studies or relevant animal studies. Pre-clinical testing should, as required, be conducted in-vitro or in animal models to investigate device biocompatibility, material properties and potential cytotoxicity according to the relevant international standards.

It is commonly argued that it is difficult to replicate in a laboratory setting how a device will perform when exposed to human subjects. However, if human subjects are to be exposed to a medical device then basic safety and performance must be demonstrated as much as is possible by pre-clinical data. It is critical that every effort is made in the pre-clinical testing to identify major device-related safety issues and that every effort is taken to ensure that unnecessary risks are avoided and unavoidable risks are minimised.

10 SPECIFIC CONSIDERATIONS FOR ETHICS COMMITTEES

Medical device clinical investigations in general involve fewer human subjects and have a shorter follow-up period than clinical trials of medicinal products. This is on the basis that the investigation is intended to ensure that the basic product performance characteristics are of an acceptable standard and do not compromise patient safety.

Additionally, device manufacturers argue that medical devices have short product life-cycles and that their devices would not be commercially viable if the same level of evidence or duration of studies were required prior to commercialisation. Nevertheless, the manufacturer must ensure that they identify risks associated with their device, minimise unavoidable risk and ensure that the benefits of using their device outweigh the associated risk. The manufacturer is required to have adequate systems in place to capture adverse events and incidents occurring during use that are associated with the device. This information should feed back into the devices safety profile and technical/design documentation.
Device investigations which involve already CE marked devices, such as post-market registry studies, generally involve larger patient numbers and longer follow up periods and are designed to gather comparative performance and safety data for a marketed device. Data gathered from post-market clinical investigations/registry studies form a crucial part of a device's long-term safety and performance profile. Device investigations of this type often do not require review by the HPRA as outlined in Section 6 of this document.

Little specific guidance for Ethics Committees exists in relation to investigations that involve medical devices. Annex X of the Medical Devices Directive (93/42/EEC) in section 2.2 Ethical considerations says “Clinical investigations must be carried out in accordance with the Helsinki Declaration...It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.” Some further generic informative guidance can be found in Annex B of the relevant international standard 'Clinical Investigations of Medical Devices for Human Subjects – Part 1: General Requirements' (ISO 14155-1:2003).

The HPRA is obliged by Article 20 of the Medical Devices Directive (93/42/EEC) to maintain confidentiality of the investigational sponsor for all clinical investigation application issues and reviews. If an Ethics Committee wished to discuss certain aspects of a specific device investigation, written permission should be obtained from the investigational sponsor to allow discussion with the HPRA.

11 DRUG-DEVICE COMBINATION INVESTIGATIONS

Increasingly medical devices are being combined with medicinal products e.g. drug-eluting coronary stents, insulin pen sets etc. For drug-device combination products the relevant legislation is applied according to the primary action of the combination.

Two examples are outlined below for example:

(i) A drug-eluting coronary stent’s primary mechanism of action is the mechanical support afforded by the stent device with the drug eluted from the stent playing an ancillary role. Any proposed clinical investigation would be subject to the requirements of the Medical Devices Directive for this combination product. However, the general principles of the medicines legislation should be applied to the drug component of the combination.

(ii) A new insulin pen system’s primary action is achieved by the drug component of the combination so the relevant medicines legislation would be applicable to any research conducted on this combination product. However, the device component should have adequate supporting data to demonstrate that it is in conformance with the Essential Requirements of the Medical Devices Directives.
12 ADVERSE EVENT REPORTING

Criteria relating to the reporting of adverse events which occur during the course of a clinical investigation should be established. These may be specifically agreed at a local level between the Ethics Committee and the investigation sponsor and may include reporting of events which occur at the local centre and also summary reporting of adverse events occurring in other international centres.

Serious adverse events and device effects should be reported by the investigator to the device manufacturer/investigation sponsor. The principles relating to what constitutes a reportable event are aligned with those of the medical devices vigilance system (reference MEDDEV 2.12-1 Rev5) and the international standard (ISO 14155 Part 1). An adverse event is deemed reportable under the medical devices legislation when either an event which led to death, serious deterioration in health, necessitated further medical/surgical intervention etc., occurred or there was the potential for such an event to occur were it not for the timely and preventative intervention of a healthcare professional or if such an event was avoided by good fortune.

Timeframes for reporting of adverse events for the medical devices vigilance system are as follows:

- Serious public health threat: immediately (without delay that could not be justified) but not later than 2 days of the manufacturer becoming aware of the threat
- Death or unanticipated serious deterioration in health: immediately but not later than 10 days
- Others: immediately but not later than 30 days

Consideration should be given to what represents anticipated versus unanticipated events which may be difficult to determine for very novel/investigational devices. The HPRA recommends that a similar timeframe is used for adverse events. The HPRA would also recommend that investigators report serious adverse events/device effects or concerns about the device to the HPRA Human Products Authorisation and Registration Department directly. Summary reporting of incidents/adverse events from other investigational centres may also be requested.
13 CLINICAL INVESTIGATION FOLLOW UP/RESPONSIBILITIES

Clinical investigators are responsible for conducting their clinical investigation according to ethical, clinical and legislative requirements. Clinical investigators must report all adverse events and device effects arising in the course of the investigation to the investigation sponsor, who in turn should inform the HPRA.

The investigator and investigation sponsor should inform the local Ethics Committee of adverse events, any proposed amendments to the clinical investigation protocol, of any reported protocol violations or if a decision is taken to cease recruitment or terminate the investigation. In these circumstances full details of the reasons for cessation of the investigation should be provided.

Particular attention should be paid to the manufacturer’s provisions for reporting of adverse events and adverse device effects that occur during the course of a clinical investigation. They should be reported both to the Ethics Committee and to the relevant Competent Authority.

14 INDEMNITY

The Clinical Indemnity Scheme (CIS) covers claims from patients whose treatment was part of a clinical investigation involving a medical device or other approved research project. In the case of clinical investigations sponsored by external organisations, such as medical device manufacturers, the CIS cover extends to treatment only and does not cover product liability or claims arising from investigation design or protocol. Cover against such claims remains the responsibility of the body conducting the clinical investigation, thus, an appropriate indemnity should be secured from the external sponsor(s).

Where the investigation is designed by an agency covered by the CIS or any of its employees (including investigator-led where the investigator is an employee), the cover under the CIS will extend to claims arising from investigational design or protocol.

In all clinical investigations involving medical devices, it is a condition precedent to CIS cover that the relevant agencies and Ethics Committee have approved the investigation.

Contact details for the State Claims Agency are provided in section 15.
15 CONTACTS

Contact details for the Clinical Assessment Section, Human Products Authorisation and Registration Department of the HPRA, as follows:

Health Products Regulatory Authority
Human Products Authorisation and Registration Department
Kevin O’Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Telephone: +353-1-6764971
Fax: +353-1-6344033
E-mail: clinicalinvestigations@hpра.ie or devices@hpра.ie

The HPRA encourages communication with the medical device sector. Should you have specific queries please address them to the Human Products Authorisation and Registration Department of the HPRA who will endeavour to be of assistance.

Communication can be made by telephone, fax, e-mail or by post to the above address.

The State Claims Agency can be contacted at:
State Claims Agency
Treasury Building
Grand Canal Street
Dublin 2
APPENDIX A: DEFINITIONS RELATING TO CLINICAL INVESTIGATIONS INVOLVING MEDICAL DEVICES

Medical Device

A medical device is defined in Article 1.2 of the Medical Devices Directive (93/42/EEC) as “…any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation or compensation of an injury or handicap,
- investigation, replacement or monitoring of the anatomy or a physiological process,
- control of conception.”

Competent Authority e.g. Health Products Regulatory Authority

The HPRA is the Competent Authority for medical devices in Ireland. There is a Competent Authority located in each Member State and approval to commence a clinical investigation must be sought from the national Competent Authority in each Member State in which a clinical investigation is to be conducted.

The role of the Competent Authority with regard to clinical investigations involving certain types of medical devices is to conduct a review of the intended purpose of the device, design aspects, technical data, benefit-risk assessment and clinical protocol design to help ensure that devices used in clinical investigations are likely to perform safely, effectively and do not pose any unnecessary risk to public health.

Applications to conduct clinical investigations involving medical devices that are submitted to the Competent Authority are primarily assessed from technical, clinical and regulatory perspectives. The Human Products Authorisation and Registration Department is composed of personnel from clinical, engineering, device industry, pharmaceutical, scientific and research backgrounds. Each application may also be reviewed by external expert(s) with specialist knowledge in the area of device use e.g. clinical specialist in the area of device use.
Clinical data gathered during the course of a clinical investigation are used by an investigation sponsor to demonstrate that their device is in conformance with the Essential Requirements of the Medical Devices Directive. This is a crucial step in the process of obtaining a CE mark for a device.

The CE mark is awarded by a Notified Body. Notified Bodies are commercial certification institutions of which there are approximately 80 throughout the EU member states. Each Notified Body has specific areas of expertise and is permitted to carry out assessment of medical devices based on their competency. Ireland has one Notified Body which is the National Standards Authority of Ireland (NSAI). Each Notified Body has a Unique Identification Number which, when applicable, appears with the CE mark to identify which Notified Body conducted the Conformity Assessment.

If a medical device is awarded a CE mark it can be marketed throughout the European Union without restriction. CE marking is typically awarded for a period of five years after which recertification must be sought from a Notified Body. Further assessment of the CE mark can take place particularly if there are major design changes or if there have been serious adverse events or episodes of device underperformance where the need for a substantial design change or next generation device has been identified.

The CE mark may also be recognised by some non-EU countries as a sign of device validation and quality.
Clinical Investigation Sponsor

The sponsor of a clinical investigation is the party responsible for the device clinical investigation. The sponsor is responsible for:

- submitting an application to conduct a clinical investigation to a specific national Competent Authority
- ensuring that the investigation is carried out according to the relevant legislation, international standards and the clinical investigation protocol
- communicating investigation amendments, protocol violations, investigation termination and adverse events to Ethics Committees and the relevant Competent Authority, when required

Medical device manufacturers typically act as sponsor for applications made to Competent Authorities, such as the HPRA, to conduct clinical investigations. The sponsor must be prepared to make all necessary data available during the review process in relation to the device and rationale for the design/parameters of the investigation. Principal investigators/clinical investigators may act as sponsor for an investigation but thereby assume all associated responsibility for the clinical investigation.

Principal Investigator / Clinical Investigator

The principal investigator involved in a device investigation is primarily responsible for designing and conducting the clinical aspects of the investigation. Commonly the principal investigation centres in medical device investigations are located in other EU Member States. The principal investigator must approve and sign the clinical investigation protocol to demonstrate their agreement with the design of the investigation and their willingness to abide by the investigation terms. Clinical investigators may be recruited at other investigation centres who report into the central group of principal investigators/sponsor. This is typically the case in investigations of medical devices in Ireland.

Serious Adverse Device Effect (as defined in ISO14155-1:2003(E))

Adverse device effect which resulted in any of the consequences characteristic of a serious adverse event or might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.
Serious Adverse Event (as defined in ISO14155-1:2003(E))

Adverse event that:
  a  led to death,
  b  led to serious deterioration in the health of the subject that:
      - resulted in a life-threatening illness or injury
      - resulted in a permanent impairment of a body structure or a body function
      - required in-patient hospitalisation or prolongation of existing hospitalisation
      - resulted in medical or surgical intervention to prevent permanent impairment to
        body structure or a body function,
  c  led to fetal distress, fetal death or a congenital abnormality or birth defect.
APPENDIX B: OVERVIEW OF LEGISLATION

There are six EU Directives concerning medical devices, as follows:

**EU Legislation governing Medical Devices**

- Directive 90/385/EEC concerning Active Implantable Medical Devices (AIMDD),
- Directive 93/42/EEC concerning General Medical Devices (MDD),
- Directive 98/79/EC concerning In-vitro Diagnostic Medical Devices (IVD’s),
- Directive 93/42/EEC as regards medical devices incorporating stable derivatives of human blood or human plasma which is to be transposed into Irish law in the near future,

The above Directives have been transposed into national law, as follows:

**National Legislation**

- S.I. No. 253 of 1994 European Communities (Active Implantable Medical Devices) Regulations, 1994 that became mandatory on 1st January 1995,
- S.I. No. 252 of 1994 European Communities (Medical Devices) Regulations, 1994 that became mandatory on 14th June 1998,
- S.I. No. 304 of 2001 European Communities (In-vitro Diagnostic Medical Devices) Regulations, 2001 that came into force on 29th June 2001 and becomes mandatory on the 7th December 2003,
- S.I. No. 444 of 2001 European Communities (Medical Devices) (Amendment) Regulations, 2001 that came into force on 1st October 2001,

- S.I. No. 576 of 2002, European Communities (Medical Devices) (Amendment) Regulations, 2002,

- S.I. No. 358 of 2003, European Communities (Medical Devices) (Reclassification of Breast Implants) (Amendment) Regulations, 2003,

- S.I. No. 554 of 2003, European Communities (Medical Devices) (Tissues of Animal Origin) Regulations, 2003,

- S.I. No. 92 of 2007, European Communities (Medical Devices) (Reclassification of hip, knee and shoulder joint replacements) (Amendment) Regulations 2007

Historically, the main purpose of the Directives was to bring about the completion of the single market by introducing harmonised controls to regulate the safety and performance of devices throughout the EU.

These Directives place explicit obligations on manufacturers who intend to place their products on the market in Ireland or elsewhere in the European Union.
APPENDIX C: SOME RELEVANT EXCERPTS FROM MEDICAL DEVICES DIRECTIVE (93/42/EEC)

The text below is taken directly from the Medical Devices Directive (93/42/EEC) which is available for download from the website of the EU Commission. Some of the references in this text, first published in 1993, have been subsequently updated e.g. Helsinki Agreement.

Article 15

Clinical investigation

1 In the case of devices intended for clinical investigations, the manufacturer, or his authorized representative established in the Community, shall follow the procedure referred to in Annex VIII and notify the competent authorities of the Member States in which the investigations are to be conducted.

2 In the case of devices falling within class III and implantable and long-term invasive devices falling within class IIIa or IIIb, the manufacturer may commence the relevant clinical investigation at the end of a period of 60 days after notification, unless the competent authorities have notified him within that period of a decision to the contrary based on considerations of public health or public policy.

Member States may however authorize manufacturers to commence the relevant clinical investigations before the expiry of the period of 60 days, in so far as the relevant ethics committee has issued a favourable opinion on the programme of investigation in question.

3 In the case of devices other than those referred to in the second paragraph, Member States may authorize manufacturers to commence clinical investigations, immediately after the date of notification, provided that the ethics committee concerned has delivered a favourable opinion with regard to the investigational plan.

4 The authorization referred to in paragraph 2 second subparagraph, and paragraph 3, may be made subject to authorization from the competent authority.

5 The clinical investigations must be conducted in accordance with the provisions of Annex X. The provisions of Annex X may be adjusted in accordance with the procedure laid down in Article 7 (2).

6 The Member States shall, if necessary, take the appropriate steps to ensure public health and public policy.

7 The manufacturer or his representative established in the Community shall keep the report referred to in point 2.3.7 of Annex X at the disposal of the competent Authorities.
The provisions of paragraphs 1 and 2 do not apply where the clinical investigations are conducted using devices which are authorized in accordance with Article 11 to bear the CE marking unless the aim of these investigations is to use the devices for a purpose other than that referred to in the relevant conformity-assessment procedure. The relevant provisions of Annex X remain applicable.

Annex VIII - Statement concerning Devices for Special Purpose

1 For custom-made devices or for devices intended for clinical investigations the manufacturer or his authorized representative established in the Community must draw up the statement containing the information stipulated in Section 2.

2 The statement must contain the following information:

2.1 for custom-made devices:

- data allowing identification of the device in question,
- a statement that the device is intended for exclusive use by a particular patient, together with the name of the patient,
- the name of the medical practitioner or other authorized person who made out the prescription and, where applicable, the name of the clinic concerned,
- the particular features of the device as specified in the relevant medical prescription,
- a statement that the device in question conforms to the essential requirements set out in Annex 1 and, where applicable, indicating which essential requirements have not been fully met, together with the grounds;

2.2 for devices intended for the clinical investigations covered by Annex X:

- data allowing identification of the device in question,
- an investigation plan stating in particular the purpose, scientific, technical or medical grounds, scope and number of devices concerned,
- the opinion of the ethics committee concerned and details of the aspects covered by its opinion,
- the name of the medical practitioner or other authorized person and of the institution responsible for the investigations,
- the place, starting date and scheduled duration for the investigations,
- a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

3 The manufacturer must also undertake to keep available for the competent national authorities:
3.1 for custom-made devices, documentation allowing an understanding of the design, manufacture and performances of the product, including the expected performances, so as to allow assessment of conformity with the requirements of this Directive.

The manufacturer must take all the measures necessary to ensure that the manufacturing process produces products which are manufactured in accordance with the documentation mentioned in the first paragraph.

3.2 for devices intended for clinical investigations, the documentation must contain:

- a general description of the product,
- design drawings, methods of manufacture envisaged, in particular as regards sterilization, and diagrams of components, sub-assemblies, circuits, etc.,
- the descriptions and explanations necessary to understand the abovementioned drawings and diagrams and the operation of the product,
- the results of the risk analysis and a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of this Directive if the standards referred to in Article 5 have not been applied,
- the results of the design calculations, and of the inspections and technical rests carried out, etc.

The manufacturer must take all the measures necessary to ensure that the manufacturing process produces products which are manufactured in accordance with the documentation referred to in the first paragraph of this section. The manufacturer must authorize the assessment, or audit where necessary, the effectiveness of these measures.

4 The information contained in the declarations concerned by this Annex should be kept for a period of time of at least five years.
Annex X – Clinical Evaluation

1 General provisions

1.1 As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I under the normal conditions of use of the device and the evaluation of the undesirable side-effects must be based on clinical data, in particular in the case of implantable devices and devices in Class III, taking account of any relevant harmonized standards, where appropriate, the adequacy of the clinical data must be based on:

1.1.1 either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed as well as, if appropriate, a written report containing a critical evaluation of this compilation.

1.1.2 or the results of all the clinical investigations made, including those carried out in conformity with Section 2.

1.2 All the data must remain confidential, in accordance with the provisions of Article 20.

2 Clinical investigations

2.1 Objectives

The objectives of clinical investigation are:

- to verify that, under normal conditions of use, the performance of the devices conform to those referred to in Section 3 of Annex I.
- to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device.

2.2 Ethical considerations*

Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the 41st World Medical Assembly in Hong Kong in 1989. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration.
This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.

2.3 Methods

2.3.1 Clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer’s claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions.

2.3.2 The procedures used to perform the investigations must be appropriate to the device under examination.

2.3.3 Clinical investigations must be performed in circumstances similar to the normal conditions of use of the device.

2.3.4 All the appropriate features, including those involving the safety and performances of the device, and its effect on patients must be examined.

2.3.5 All adverse incidents such as those specified in Article 10 must be fully recorded and notified to the competent authority.

2.3.6 The investigations must be performed under the responsibility of a medical practitioner or another authorized qualified person in an appropriate environment. The medical practitioner or other authorized person must have access to the technical and clinical data regarding the device.

2.3.7 The written report, signed by the medical practitioner or other authorized person responsible, must contain critical evaluation of all the data collected during the clinical investigation.

* The Helsinki Agreement has been subsequently updated and is currently undergoing an extensive revision. This text is taken directly from the Medical Devices Directive (93/42/EEC)
APPENDIX D: FURTHER READING

1. ISO 14155 Parts 1 & 2: Clinical Investigations involving medical devices in human subjects

2. 93/42/EEC General Medical Devices Directive

3. HPRA Guidance Note 5: Guidance Note for Manufacturers of Clinical Investigations carried out in Ireland

4. HPRA Guidance Note 7: Guidance Note on the Vigilance System for Medical Devices

5. MEDDEV 2.12-1 Guidelines on a medical devices vigilance system

6. 90/385/EEC Active Implantable Medical Devices Directive


Many of these documents can be downloaded from the HPRA website. Please see the ‘Publications and Forms’ section of www.hpra.ie

Another useful source of documentation is the website of the European Commission.