Medical Devices - IRELAND

Competent authority

Contact Details

Contact Name 1

Health Products Regulatory Authority HPRA (formerly known as Irish Medicines Board IMB- up to July 2014)

Phone

+353-1-6764971

Fax

+353-1-6767836

Email General

info@hpra.ie

Email Department

devices@hpra.ie

Address

Kevin O´Malley House/ Earlsfort Centre/ Ealsfort Terrace

ZIP/City

Dublin 2 (Post code: D02 XP77)

Country

Ireland (IE)

Web address

http://www.hpra.ie

Additional Information

Email: devices@hpra.ie for submission of clinical investigation applications

No local CA.

Trial Authorisation / Registration / Notification

Regulatory and ethics bodies involved in approval process

Competent Authority/-ies (CA)/ For certain types of MDs
Ethics committee(s)

CA - Submission for authorisation mandatory for

MD CE-marked, use outside label
MD CE-marked, use outside label + IMP
MD without label
MD without label + IMP
NB: Pre-submission meetings with potential sponsors of clinical investigations are encouraged by HPRA

CA - Registration/ notification without approval required for

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CA - Submission required to

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CE-marked MD used within label are exempted from any notification obligation to CA

Yes

Additional Information

Only certain types of clinical investigation involving MD require notification and review by the HPRA prior to commencement:

(1) Clinical investigations that are likely to require notification and review by the HPRA prior to commencement include:
- New devices
- Modification of an existing device
- Device containing untested materials
- Device materials used in a different location or for a different duration
- Device proposed for a new function

Related details are specified in the guidance document describing the circumstances when notification and review are required: 'Guide for Manufacturers and Sponsors on Clinical Investigations Carried out in Ireland' (available on the HPRA website in section: About us>Publications&Forms>Guidance Documents)
Any queries regarding the type of device investigations requiring notification and review can be submitted to HPRA.

(2) 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.

(3) In-vitro diagnostics: It should be noted that there is no specific legislation relating to clinical investigations involving in-vitro diagnostic medical devices. Rather, in-vitro diagnostic medical devices have to undergo performance evaluation as specified under Annex VIII of the In-vitro Diagnostic Medical Devices Directive 98/79/EC.

Submission to CA and EC to be performed in the following order

In parallel

Submission of Application

Responsible for study submission

Sponsor
Manufacturer acting as sponsor
(Typically, applications are submitted by medical device manufacturers)

Entitled to study submission

–

Prerequisites for submission

–

Guidance on submission of application available

Yes

Guidance on submission of application

'Guide for Manufacturers and Sponsors on Clinical Investigations Carried out in Ireland', available on the HPRA website in section: About us>Publications&Forms>Guidance Documents.

Additional Information

Clinical investigation applications will receive a unique identification number, CIV ID, (if not previously assigned) for the purposes of notification to the EUDAMED database from the HPRA.

Submission Format	**Format option(s)** Email Data carrier (CD-rom/DVD) **Preferred format** The HPRA strongly recommends electronic submission by e-mail or on CD/DVD. Electronic submissions are acceptable in Word or pdf format. **Standard application form available** Yes **Standard application form** 'Application for Clinical Investigations on Medical Devices' form (available at HPRA website in section: Medical Devices>Regulatory Information>Clinical Investigations). **Standard application form - Additional information** An application for a clinical investigation consists of the following: - A completed 'Application for Clinical Investigations on Medical Devices' form - any required documentation (ist provided in application form) - the relevant fee **Guidance on submission format** Further guidance on the format of electronic submissions, including file naming conventions, are described in 'Guide for Manufacturers and Sponsors on Clinical Investigations Carried out in Ireland', available on the HPRA website in section: About us>Publications&Forms>Guidance Documents. **Additional Information** Submission cut of dates: The list of monthly cut-off dates for submission of clinical investigation applications are published on the HPRA website in section: Medical devices>Regulatory Information>Clinical Investigations
Language of Submission	**Language(s) of application** English **Preferred language of application** – **English accepted** – **Documents mandatory to be in official national language** – **Documents mandatory to be in local language of study site** – **Documents mandatory to be in language of the study participant** – **Additional Information** All applications (including the supporting data) must be in English.
Submission Fees	**Fees for trial submission mandatory** Yes

	Fees Fees published for 2015 are provided below as a guide, but should be checked for currency at time of application: - Active implantable medical devices €3,837. - Class III and class IIb medical devices €3,837. - Class IIa and class I medical devices €1,645. - Technical amendment: €1,129. - Administrative amendment (e.g., additional investigational site): € 219. - Resubmission following a withdrawal or objection: €1,500. No fees are charged for academically sponsored investigations. (Reduced fee for Resubmission for Academic Sponsor: €500). **Official guidance on required fees** The current fees are provided in the “Fee Application Form for Human Products” and the respective “Guide to Fees for Human Products”, being available for download on the HPRA website in section Medical Devices>Regulatory Information> Clinical Investigations. **Applicable national legal framework/ Reference** Fees for applications are laid down in the HPRA (Fees) Regulations, which are made each year by the Minister for Health.
Timelines Authorisation	**General timespan (max nr days)** 60 **Mode of approval (General)** Explicit (written) In case of positive outcome, CA issues “Letter of no objection” **Timespan counted from** Date of receipt of valid application **Applicable national legal framework/ Reference** Timelines for the review procedure are described in ‘Guide for Manufacturers and Sponsors on Clinical Investigations Carried out in Ireland’, available on the HPRA website in section: About us>Publications&Forms>Guidance Documents. **Additional Information** ad Approval procedure: Applications are validated on receipt, and start of the procedure is held pending submission of any additional information. Once validated, HPRA provides an initial 30-day review. Further information may be requested from the manufacturer. Response must be submitted within 14 days. The manufacturer will be notified of the outcome by day 60. NB: The final opinion of the Ethics Committee must be submitted to the HPRA prior to the HPRA finalising its review (and prior to commencement of the investigation).
Amendments/ Substantial Amendments (SA)	**Notification mandatory for** – **Authorisation mandatory for** All changes in the protocol (relating to the device, aspects of clinical investigation plan, investigator, or investigation sites) **Responsible for submission of SA** – **Standard notification form available** Yes

Standard notification form

A standard application form ('Application for Amendments to Clinical Investigations on Medical Devices') is available on the HPRA website in section Medical Devices>Regulatory Information> Clinical Investigations.

Timeline for approval of SA (max nr days)

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Additional Information

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 CA 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.

Safety Reporting

Responsible for AE reporting to CA

Sponsor

Sponsor must declare reportable events to

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Reportable AEs

SAE (Serious Adverse Event)
SAE (Serious Adverse Event) including AE being life-threatening or leading to death or to a serious deterioration in health, prolonged hospitalisation, additional surgery or medical intervention
Device deficiency, that might have led to SAE if no action or intervention had been made

SUSAR being life-thereatening or leading to death must be reported

–

All other SUSARs

–

SAE /SADE must be reported

–

National standard reporting form available

–

Reporting format - Options

The HPRA contact address for SAE reporting of clinical investigations will be communicated directly to the sponsor

Preferred format

–

Provision of Annual safety report mandatory

No

Annual safety report shall be provided by sponsor to

–

Guidance on AE reporting procedure

Reporting to HPRA should follow instructions given in the ‘Guide for Manufacturers and Sponsors on Clinical Investigations Carried out in Ireland’ (available on the HPRA website in section: About Us > Publications&Forms > Guidance Documents

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 accept summary tabulations of serious adverse events as outlined in this document, however may request more specific information on specific serious adverse events if deemed necessary.

National legal framework in place

Yes

Applicable national legal framework/ Reference

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.

Additional Information

- Reporting timelines: Timelines for reporting may occasionally be amended by HPRA, depending on the nature of the clinical investigation by notification of HPRA to the sponsor.

- Annual safety report: Annual safety report is not needed for clinical investigations unless it is specifically requested as a condition to the ‘letter of no objection’.

- Post market clinical follow-up study on a CE marked device used within its indication: the sponsor of this study should report according to the MEDDEV guidance series 2.12 on market surveillance.

Investigator shall report SAE to

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Reporting timeline

–

End of Trial

End of trial declaration mandatory for

All clinical investigations requiring authorisation by CA

Responsible for End of trial declaration

Manufacturer
Legal representative

Regular Termination - Declaration timespan (max nr days)

3 month of the completion of the investigation, unless otherwise agreed in writing.

Timespan counted from

–

Early/premature Termination - Declaration timespan (max nr days)

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Additional Information

The manufacturer or the authorised representative must prepare a written report on completion of the clinical investigation.
Format: hard copy or electronic.

Ethics committee

Contact Details	**Contact Name 1** Local Research Ethics Committees (RECs) **Contact Name 2** Contact details for the ethics committee affiliated to an institution should be sought from the site of the proposed investigation **Web address** http://www.molecularmedicineireland.ie/home **Additional Information** Contact details for those ethics committees which use the Research Ethics Committee Standard Application Form (RECSAF) are documented in the Standard Appliation Form Guidance Manual For Applicants (versoin 5.6), available from the 'Molecular Medicine Ireland' website in section: Clinical Research/ REsearch Ethics (see link provided in address field) No central EC.
Ethical Review – General	**Submission for Ethical review mandatory for** All clinical investigations of MD **Submission to CA and EC to be performed in the following order** In parallel **Additional Information** If a clinical investigation does require notification and review, the application may be submitted in parallel with Ethics Committee(s) review. NB! The final opinion of the Ethics Committee must be submitted to the HPRA prior to the HPRA finalising its review (and prior to commencement of the investigation). **Regulatory and ethics bodies involved in approval process** Competent Authority/-ies (CA)/ For certain types of MDs Ethics committee(s)
Single-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) to be obtained from** Local EC linked to the trial site **Additional Information** All clinical investigations of MD shall be submitted to the relevant local institutional EC for ethical review.
Multi-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) required from** All local ECs of participating sites **Submission of application required to** All local ECs of participating sites **Additional Information** In the case of multi-centre clinical investigations, opinions must be obtained from the ethics committee of each participating centre. Only those centres that have provided the local ethics committee opinion to HPRA may commence clinical investigation when no objection has been raised by the HPRA.

Submission of Application	**Responsible for study submission** Sponsor Manufacturer acting as sponsor Principal Investigator **Entitled to study submission** – **Prerequisites for submission / approval** –
Submission Format	**Format option(s)** The local ethics committee should be referred to for the preferred format. **Preferred format** – **Standard application form** There is a standard form for clinical investigations of MD and other health-related research studies which are not clinical trials of medicinal products for human use as defined in SI 190/2004, which is used by a number of ECs. Some local ethics committees may request a different format. The "Standard Application Form RECSAF (Version 5.6)" is available on the Molecular Medicine Ireland website and from research ethics committees. Related information and detailed guidance is provided in the accompanying “Guidance Manual- Standard application form” available on the MMI website.
Language of Submission	**Language(s) of application** English **Preferred language of application** – **English accepted** – **Documents mandatory to be in official national language** – **Documents mandatory to be in local language of study site** – **Documents mandatory to be in language of study participant** –
Submission Fees	**Fees for Ethical review mandatory** Yes **Fees for Ethical review** It varies by ethics committees. Range is of the order of €150-1500.
Timelines Ethical Review	**General timespan for single-centre studies (max nr days)** 60 Timelines can vary depending on EC **General timespan for multi-centre studies (max nr days)** 60 Timelines can vary depending on EC

	External expert advice required: Timespan (max nr days) – **Timespan counted from** – **Additional Information** The final opinion of the Ethics Committee must be submitted to the HPRA prior to the HPRA finalising its review and commencement of the investigation.
Amendments/ Substantial Amendments (SA)	**Ethical review mandatory for** Any amendments **Responsible for notification of SA** – **Standard notification form available** No **Standard notification form** The local EC should be referred to for the required format of the amendment submission. **Timeline Ethical review of SA (max nr days)** – **Guidance on submission of SA available** No **Guidance on submission of SA** The local EC should be referred to for the required format of the amendment submission.
Safety Reporting	**Reportable AEs** SAE (Serious Adverse Event) SADE (Serious Adverse Device Effect) **Investigator shall report SAE to** – **Reporting timeline** – **Responsible for AE reporting to relevant EC(s)** – **SUSAR being life-thereatening or leading to death must be reported** – **All other SUSAR must be reported** – **SAE/SADE must be reported** – **National Standard Reporting form available** – **Reporting format - Options** –

Preferred reporting format

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Additional Information

All serious adverse events, including device events, occurring during the course of a research study must be reported as per each committee's local guidelines in this matter. Serious Adverse Events should be reported in line with each committee's local definitions, format and timelines.

End of Trial

End of trial Declaration mandatory

Yes

Responsible for End of trial Declaration

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Regular Termination - Declaration timespan (max nr days)

Each local EC should be referred to for institutional requirement.

Timespan counted from

–

Early/premature Termination - Declaration timespan (max nr days)

Each local EC should be referred to for institutional requirement.

Standard Declaration form available

No

Standard Declaration form

Format: Each local EC should be referred to for institutional requirement. However, in general a final progress report, as foreseen by the Helsinki Declaration, should be submitted.

Guidance on End of trial declaration available

No

Guidance on End of trial declaration

Each local EC should be referred to for institutional requirement

Additional Information

Procedure of declaration: Each local EC should be referred to for institutional preferred practice.

Study specific Requirements

Sponsor

Sponsor - Definition (pursuant to national law)

The sponsor of a clinical investigation is the party responsible for the device clinical investigation, e.g. the manufacturer, academic group, clinical research organisation.

Manufacturer's typically act as sponsor for applications made to the CA (if the manufacturer is not based in Europe the name, address telephone fax e-mail address of the authorised representative must be provided)
Principal investigators/clinical investigators may act as sponsor for an investigation but thereby assume all associated responsibility for the clinical investigation.

Co-Sponsor - Definition available in national law

No

Legal representative based in the EU/EEA is mandatory where Sponsor is located outside EU/EEA:

Yes

Study Participants - Informed Consent (IC)

Standard IC form (ICF) available

Not specified

IC is regulated by law

Yes

Informed Consent - Definition/ Requirements

In accordance with S.I No. 252/1994, as amended by S.I No. 110 of 2009, all clinical investigations must be carried out in accordance with the Helsinki Declaration, including those measures relating to the protection of human subjects, such as informed consent. Further guidance on obtaining informed consent for research purposes are provided in Section 2-5 of HSE National Consent Policy Part 3 Research.

Study Participants - Vulnerable Population

Minors / Children - Studies allowed

Yes
No explicit provisions in national legislation

Specific provision

For all research other than clinical trials, a person must be over the age of 18 years in order to provide consent to participate in research. It is strongly recommended that expert advice is sought where the research study involves persons between the age of 16-18 years.

Further guidance on the specific provisions which apply to the types of research that can be performed in minors is provided in Section 3 of HSE National Consent Policy Part 3 Research. The guidance also provides further information on the matter of consent.

In accordance with S.I No. 252/1994, as amended by S.I No. 110 of 2009, all clinical investigations must be carried out in accordance with the Helsinki Declaration, including those measures relating to the protection of human subjects, such as informed consent.

Incapacitated persons - Studies allowed

Yes
No explicit provisions in national legislation

Specific provisions

In accordance with S.I No. 252/1994, as amended by S.I No. 110 of 2009, all clinical investigations must be carried out in accordance with the Helsinki Declaration, including those measures relating to the protection of human subjects, such as informed consent. Outside of clinical trials, there is currently no specific legal provision(s) for the participation of an incapacitated person in research. The HSE National Consent Policy recommends that, in the absence of legislation, as a matter of best practice the same principles as those which apply to clinical trials should be applied. This means that consent for participation in any form of research on behalf of an incapacitated person must be obtained from the person's legal representative. However, this approach does not have a legislative/legal basis. Further guidance is available in Section 4 of HSE National Consent Policy Part 3 Research. The proposed approach should be clearly detailed in the ethics application.

Emergency situations - Studies allowed

Yes
No explicit provisions in national legislation

	Specific provisions In accordance with S.I No. 252/1994 , as amended by S.I No. 110 of 2009 (www.irishstatutebook.ie), all clinical investigations must be carried out in accordance with the Helsinki Declaration, including those measures relating to the protection of human subjects, such as informed consent. Outside of clinical trials, there is currently no specific legal provision(s) for subjects in emergency situations. However, guidance is given in Section 5.1.of HSE National Consent Policy Part 3 Research, regarding the handling of consent in such situations and the type of research that can be performed. Reference should also be made to the Helsinki Declaration, as required by national legislation. The proposed approach should be clearly detailed in the ethics application. **Emergency situation without prior consent of patient or proxy - Studies allowed** No explicit provisions in national legislation **Pregnant or breastfeeding women - Studies allowed** No explicit provisions in national legislation **Specific provisions** There is no specific legal provisions dealing with pregnant or lactating women. Ethics Committees should be informed if pregnant or lactating women are proposed to be recruited to a study. **Guidelines & conventions for protection of vulnerable populations** Section 3-5 of HSE National Consent Policy Part 3 Research
Study Participants - Compensation & Reimbursement	**Reimbursement for study participants** Permissible **Compensation is limited to/provided for** Time Expenses (e.g. transportation, meals, and others such as salary lost) **Additional Information** According to Section 13 of HSE National Consent Policy Part 3 Research, reimbursement for lost earnings, travel costs and other expenses incurred as well as compensation for the time and inconvenience involved in research participation (e.g. payment at minimum wage levels) might be permissible as research participants should not be expected to bear the costs that relate to taking part in a study. However, it is important to note that compensation is understood to mean a recompense for losses sustained e.g. time away from work.
Data Protection	**Notification to DP Authority/ Ombudsmann is mandatory** No **Specific notification timelines before operations start** – **Language of notification** – **Notification format** – **Data Protection Authority/ Agency - Contact Details** Office of the Data Protection Commissioner

	Contact Name 2 Contact details are available from the website: **Web address** http://www.dataprotection.ie/ **Country** Ireland (IE) **Additional Information** The rights of each study participant to physical and mental integrity, to privacy and to the protection of the data concerning him or her are safeguarded in accordance with the Data Protection Acts 1988 and 2003. **Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)** National Data Protection Act **National DP act** The main Irish law dealing with data protection is the Data Protection Act 1988. The 1988 Act was amended by the Data Protection (Amendment) Act 2003.
Insurance	**Liability insurance or alternative arrangements for damages mandatory for** Sponsor Hospital/ trial center **Responsible for covering insurance** – **Additional Information** Appropriate insurance/indemnity for the research study at each site, as well as for the organisation legally responsible for the initiation and management of the study (if different) will be required. Evidence, including certificates of insurance, will be subject to assessment by the local ethics committee. Of note, public health facilities will be covered under the state sponsored Clinical Indemnity Scheme (CIS) for the majority of research. 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 between the site and the external sponsor(s). Private healthcare facilities are also outside of the CIS cover, and must provide their own privately held medical/clinical malpractice insurance policy. Related information is provided on the MMI website in the Standard Application Form Guidance Manual For Applicants (version 5.6) or the HPRA Guide for Ethics Committees on Clinical Investigation of Medical Devices. 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. Further information is available from the State Claims Agency.
Quality Assurance/ Quality Control (QA/QC)	**Monitoring** Compulsory **Audit by sponsor** Compulsory

Standard Operating Procedures (SOPs)

Compulsory

Additional Information

Clinical investigations are subject to controls equivalent to the requirements of the relevant European standard (EN ISO 14155:2011)

National legislation

General Information: Applicable Legislation & Conventions

Official website providing relevant national legislation available

Yes

Official website providing relevant national legislation

An overview on applicable laws, regulations and amendments is available on the HPRA website in section Legislation.

Official governmental legal database available

Yes

Official governmental legal database

Irish Statute Book: Public legal database by the Office of the Attorney General (the chief law officer of the State)

Investigations on Medical Devices

Applicable national regulations

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Transposition of Directive 90/385/EEC

S.I. No. 253 of 1994, as amended (transposing Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC, as amended)

Directive 2007/47/EEC (transposed as S.I no. 110 of 2009) introduced relevant changes for implantable and Class III devices and the rules for clinical investigations, amending the principal regulation S.I no. 253 of 1994.

Transposition of Directive 93/42/EEC

S.I. No. 252/1994, as amended (transposing Medical Devices Directive (MDD) 93/42/EEC, as amended)

S.I no.110 of 2009 (transposing Directive 2007/47/EEC) amending the principal regulation S.I no. 252 of 1994.

Transposition of Directive 98/79/EC

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

Additional Information

The principles of clinical investigation of medical devices, excluding IVDs, are set out in the European standard ISO 14155:2011. 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.

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.

Combination Studies (IMP&MD)

Applicable national regulations

Depending on whether considered as MP or MD

	Additional Information For drug-device combination products the relevant legislation is applied according to the primary action of the combination.
Radiation & Radiotherapy	**Use of radiation or radioactive compounds - Specific requirements** Yes **Applicable legal framework** S.I. No. 478/2002 - European Communities (Medical Ionising Radiation Protection) Regulations 2002 S.I. No. 125/2000 - Radiological Protection Act, 1991 (Ionising Radiation) Order, 2000
Data Protection	**Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)** National Data Protection Act **National DP act** The main Irish law dealing with data protection is the Data Protection Act 1988. The 1988 Act was amended by the Data Protection (Amendment) Act 2003.

Definition

MD/MD Investigation	**MD - Definition available in national law** Yes **MD - Definition** Definitions according Regulation (2) of S.I No. 110 of 2009, amending the Principal Regulation S.I No. 252/1994: (1) “device” means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: (i) diagnosis, prevention, monitoring, treatment or alleviation of disease, (ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, (iii) investigation, replacement or modification of the anatomy or of a physiological process, or (iv) control of conception; and (v) does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means; (2) “intended for clinical investigation” means, in relation to a device, that it is — (a) intended for use by a registered medical practitioner user when conducting investigations of that device in an adequate human clinical environment; or (b) for use by any other person who by virtue of his or her professional qualifications is authorised to carry out investigations of that device in an adequate human clinical environment; **Investigation of MD - Definition available in national law** No **Investigation of MD - Definition** Clinical investigation (Definition according to ISO Standard 141555:2011): “... any designed and planned systematic study in human subjects undertaken to verify the safety and/or performance of a specific device”