ECRIN
EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK
IA-Integrating Activity

Regulatory and ethical requirements in medical device studies

Ireland

SECTIONS

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A. Type of research

We have differentiated 8 types of research:

- Medical device alone with CE mark use within label
- Medical device alone with CE mark use outside label
- Medical device alone without CE mark
- Medical device combined with medicinal product with CE mark use within label
- Medical device combined with medicinal product with CE mark use outside label
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Definitions in Irish law

The following are sources of information defining clinical research in medical device studies in Ireland

- Health Products Regulatory Authority (www.hpra.ie)
- Irish Statute Book (www.irishstatutebook.ie)

Conventions/guideline/laws to apply

- All research studies should be performed according to the Declaration of Helsinki.

- Clinical Investigations are governed by European Directives, transposed into National Statutory Instruments (S.I, see www.irishstatutebook.ie), as follows:
  - AIMDD 90/85/EEC transposed as S.I no. 253 of 1994
  - MDD 93/42/EEC transposed as S.I no. 252 of 1994
  - IVD MDD 98/79/EEC transposed as S.I no. 304 of 2001
  - Directive 2007/47/EEC transposed as S.I no. 110 of 2009, and which substantially amended the principal regulations noted above

Note! for drug-device combination products the relevant legislation is applied according to the primary action of the combination. If the primary action is device, the above legislation will apply. If the primary action is medicinal, the research may be governed by the CT and GCP Directives.

Conventions/guideline/laws to apply

- National guidelines:
  - The HPRA '*Guide for Manufacturer's and Sponsors on Clinical Investigations carried out in Ireland*', see www.hpra.ie
  - The HPRA '*Guide for Ethics Committes on Clinical Investigation of Medical Devices*', see www.hpra.ie
  - *'Guidance manual for the standard application form for the ethical review of health related research studies which are not clinical trials on medicinal products for human use as defined in Statutory Instrument 190/2004',* prepared by the Standard Application Form Consultation Group, see www.molecularmedicineireland.ie/research_ethics
- Standards:
  - ISO 14155:2011 Clinical Investigations
  - MEDDEV2.7/3, Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting

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C. Insurance

- Appropriate insurance/indemnity for the research study at each site is required.

- Public health facilities are covered under state sponsored Clinical Indemnity Scheme (CIS) for the majority of research (www.stateclaims.ie).

- In case of clinical investigations sponsored by external organisations, CIS extends to treatment only and does not cover product liability or claims arising from investigation design/protocol. As such, an indemnity should be secured between the site and external sponsor.

Note! Insurance certificates/indemnity arrangements are subject to review by the Ethics Committee.

C. Insurance

- Private health facilities does not fall under the CIS, and must provide cover, including medical/clinical malpractice.
- For clinical investigations, insurance is also required for the organisation legally responsible for the initiation and management of the study (i.e. manufacturer/sponsor).
- There is no mandatory compensation sum per participant or per trial. However, it is generally advised that the trial is insured for a minimum sum of 6.5 million euro.

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- The manufacturer normally acts as the sponsor of a clinical investigation.
- If not based in the Community, the manufacturer should have an authorised representative that is based in the Community.
- A distinction is drawn 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.

D. Sponsor

- 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.

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- 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.

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E. Investigators

Training of Investigators:

- There are no specific national requirements/regulations for GCP training of Investigators in Ireland for any of the study types.
- However, it is recommended that guidance given in ISO 14155:2011 with respect to training, qualifications and experience should be followed.

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F. Competent Authority

Irish Competent Authority:

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

Address: Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland

Website: http://www.hpra.ie

Telephone: +353 1 676 4971

Email: info@hpra.ie or devices@hpra.ie

F. Competent Authority

	Approval	
	Yes	No
Medical device alone with CE mark use within label		x
Medical device alone with CE mark use outside label	x	
Medical device alone without CE mark	x	
Medical device combined with medicinal product with CE mark use outside label	x	
Medical device combined with medicinal product without CE mark	x	

Note! See HPRA 'Guide for Manufacturers and Sponsors on Clinical Investigations carried out in Ireland' for further information on the types of investigations which may require notification. The Guide is available on www.hpra.ie, under publications&forms, guidance documents.

F. Competent Authority – Initial submission

- The sponsor/manufacturer is responsible for the submission to the HPRA.
- The submission is national i.e. *you submit one dossier to the national competent authority, HPRA.*
- Electronic submission is strongly recommended, by email or on CD/DVD. *Note! See HPRA website for further information on file naming conventions.*
- *Note! HPRA strongly recommend a pre-submission meeting*
- English documents are accepted.
- A fee is payable. Fees for the current year are available from HPRA '*Guide to Fees for Human Products, which is published*' on the HPRA website.

F. Competent Authority – Initial submission

- There is a standard application form - see link below: http://www.hpra.ie/homepage/medical-devices/regulatory-information/clinical-investigations

- The assessment procedure is as follows:
  - Applications are validated on receipt.
  - Once validated, HPRA provides an initial 30 day review.
  - Further information may be requested.
  - The manufacturer will be notified of the outcome by Day 60 of the review.

F. Competant Authority – Initial submission

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A list of documentation required to support the submission is given in the application form. The main documents are:

- Complete application form
- A copy of the opinion of the local ethics committee(s) concerned on the details of the aspects covered by its opinion
- Copy of informed consent
- Data allowing identification of device (i) generic name (ii) model name (iii) model number i.e. label, instruction for use
- General description of product
- An investigation plan
- Criteria for patient selection
- Number of patients in clinical investigation
- Design drawings methods of manufacture envisaged and description
- Risk analysis results
- Design calculation result, including of inspections and tests carried out
- Summary of experience with any similar device
- Details of new or previously untested features
- Photograph of the device

F. Competent Authority - Vigilance

- 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: led to death, 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, led to fetal distress, fetal death or a congenital abnormality or birth defect.

F. Competent Authority - Vigilance

- 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 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

F. Competent Authority – Substantial amendment

- There is a specific procedure for submitting a substantial amendment to the HPRA
- 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.

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G. Ethics Committee

- A positive opinion of an Ethics Committee (EC) is required for all types of research involving medical devices.
- For research involving mutiple centres in Ireland, an opinion is required from each relevant EC involved.
- For clinical investigations requiring notification to HPRA, the full opinion of the EC must be submitted to the HPRA prior to the HPRA finalising its review.
- The submission to the EC can be made in parallel to the HPRA.

G. Ethics Committee

	Positive opinion required	
	Yes	No
Medical device alone with CE mark use within label	x	
Medical device alone with CE mark use outside label	x	
Medical device alone without CE mark	x	
Medical device combined with medicinal product with CE mark use within label	x	
Medical device combined with medicinal product with CE mark use outside label	x	
Medical device combined with medicinal product without CE mark	x	
Observational studies with medical device	X	
Registries	x	

G. Ethics Committee – Initial submission

- The Investigator is responsible for making the submission to the EC.
- The submission is local (*i.e. made to the relevant ethics committee for each site involved*).
- The submission criteria for each local EC are similar, however, there are variations. Consult with the relevant EC prior to submission to confirm details.
- The documents must be submitted in English.
- There is a submission fee, which varies by EC, ranging from 150 to 1500 euro.

G. Ethics Committee – Initial submission

- Assessment procedure:
  - The timespan for approval varies but is generally 60 days
  - Some EC may have submission deadlines/cut off - *consult with the local EC to identify if this is the case*
- When both HPRA approval and EC positive opinion are required, it is possible to submit in parallel.
- When manufacturer is not based in Europe, the name, address, telephone, fax and email address of the authorised representative must be provided.

G. Ethics committee – Initial submission

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- There is a standard application form which is accepted by a number of the ECs.
- However, this should be confirmed prior to submission.
- The form is called the Research Ethics Committee Standard Application Form (RECSAF).
- It is available from www.molecularmedicineireland.ie/research_ethics

G. Ethics Committee – Initial submission

- The documentation required to accompany the application form can vary by EC. Therefore, it is best to consult with each relevant EC to determine current list during submission preparation.
- However, general information on the type and scope of documentation required is provided in the *'Guidance manual for the standard application form for the ethical review of health related research studies which are not clinical trials on medicinal products for human use as defined in Statutory Instrument 190/2004',* prepared by the Standard Application Form Consultation Group.
- The above guidance document is available from: www.molecularmedicineireland.ie/research_ethics

G. Ethics Committee - Vigilance

- Vigilance: criteria are established by the EC for the reporting of Adverse Events (AEs) which occur during the course of a clinical investigation.

- AE, ADE, SADE and SAE:
  - The EC will have criteria for reporting of AEs which occur at the local level.
  - Summary reporting of AEs from other centres may also be necessary.

G. Ethics Committee – Substantial amendment

- In general, any amendment to the research study should be subject to review by the relevant EC.
- Consult with the relevant EC regarding specific local requirements.

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H. Data Protection

- 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

- Data Protection Agency:
  - Office of the Data Protection Commissioner, Canal House, Station Road, Portarlington, Co. Laois, Ireland
  - Tel +353 57 868 4800
  - Email: info@dataprotection.ie
  - *https://www.**dataprotection**.ie/*

H. Data Protection

	Notification required	
	Yes	No
Medical device alone with CE mark use within label		X
Medical device alone with CE mark use outside label		X
Medical device alone without CE mark		X
Medical device combined with medicinal product with CE mark use within label		X
Medical device combined with medicinal product with CE mark use outside label		X
Medical device combined with medicinal product without CE mark		X

Notification is not required per study. However, Data Controllers are required to register with the Office of the Data Protection Commissioner. Further information is available from https://www.dataprotection.ie/ViewDoc.asp?fn=/documents/guidance/Guide_Data_Contollers.htm&CatID=90&m=y

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I. Healthy volunteers/Patients

- In Ireland, there are no specific national legal requirements/regulations for the following patient populations: Children, pregnant and lactating women, incapacitated adults, emergency situations.
- However, researchers are required to adhere to the Declaration of Helsinki, including provisions laid down in respect of the above patient populations.
- Details of the patient population, in particular vulnerable populations, will also be required by the EC.

I. Healthy volunteers/Patients

- There is a National Policy on Consent, published by the State Health Services Executive (HSE), which includes best practice for research involving human subjects, including vulnerable populations.

- The policy is available from: http://www.hse.ie/eng/about/Who/qualityandpatientsafety/National_Consent_Policy/consent.html

I. Healthy volunteers/Patients

- There are no specific legal requirements in Ireland regarding compensation fees for subjects participating in clinical research.

- However, in general, plans to compensate subjects are reviewed as part of the EC assessment. The following guidance is given in the Manual for the Standard Ethics Application Form in relation to payment to participants:

'There may be instances where research participants will be paid for any inconvenience and time given to the study. Payments may be financial or non-financial. Payment that is disproportionate to the time involved or is likely to encourage participants to take risks, is ethically unacceptable. The timing of payments must be such that they do not constitute under inducement'.

- There is no national register of healthy volunteers in Ireland.

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- Further information and support with regard to medical device research is available from the Health Research Board Clinical Research Coordination Ireland (HRB CRCI) Group. See www.hrb-crci.ie for further information.

- Device investigations conducted as part of academic/non commercial research may attract HPRA fee reductions/waivers. *See HPRA 'Guide for Manufacturers and Sponsors on Clinical Investigations carried out in Ireland' for further information on the types of investigations which may require notification. The Guide is available on www.hpra.ie, under publications&forms, guidance documents.*