Medicinal Products for Human Use - IRELAND

Competent authority

Contact Details	**Contact Name 1** Health Products Regulatory Authority (HPRA) **Contact Name 2** (formerly known as Irish Medicines Board IMB- up to July 2014) **Phone** +353-1-6764971 **Fax** +353-1-6767836 **Email General** info@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** • HPRA Receipts and Validation section: submissions@hpra.ie (for Application for authorisation, amendments, and DSURs) • Clinical Trials Unit: clinicaltrials@hpra.ie (for Submission of urgent safety restriction, end of trial declarations, reports, responses to grounds for non-acceptance letters • Pharmacovigilance section: medsafety@hpra.ie (for AE/ SUSAR reporting) No local CA.
Trial Authorisation / Registration / Notification	**Regulatory and ethics bodies involved in approval process** Competent Authority/-ies (CA) Ethics committee(s) **CA - Submission for authorisation mandatory for** All clinical trials on Medicinal Products (MP) **CA - Registration/ notification without approval required for** – **CA - Submission required to** National CA

Submission of Application	**Responsible for study submission** Sponsor Legal representative **Entitled to study submission** – **Prerequisites for submission** – **Guidance on submission of application** A detailed guidance for sponsors entitled “Guide to Clinical Trial Applications” is available on the HPRA website in section: Medicines>Regulatory Information>Clinical trials>Clinical Trial Applications (www.hpra.ie). It covers in detail the legal framework, the submission procedure and all other relevant requirements on amendments, safety reporting and trial termination. **Applicable national legal framework/ Reference** Regulation 14 SI 190/2004 Applications should comply with the European Commission’s guideline (CT-1). **Additional Information** NB! Clinical trials meeting dates: The Clinical Trials Sub-committee of HPRA meets monthly to review all clinical trial applications. The list of monthly cut-off dates are published on the HPRA website in section: Medicines>Regulatory Information>Clinical trials>Clinical Trial Applications (www.hpra.ie). Applications submitted at any stage over the month before 5:00 pm on the cut-off date will be reviewed at the subsequent CT Sub-committee meeting. GMO: If any product used in the trial is a genetically-modified organism, a separate application for a licence must be made to the Environmental Protection Agency. A copy of the licence from the agency should be provided with the clinical trial application.Information on clinical trials using medicinal products containing genetically-modified organisms is available from the Environmental Protection Agency (see ‘GMO Part B Deliberate Release’) Voluntary Harmonisation Procedure: A sponsor may also use the VHP process for multinational trials involving Ireland. In this case detailed information on the process and requirements is provided in ‘Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications’ on the HMA website (www.hma.eu).
Submission Format	**Format option(s)** Electronically to HPRA Receipts and Validation section: submissions@hpra.ie (strongly recommended by HPRA!) **Preferred format** –
Language of Submission	**Language(s) of application** English **Preferred language of application** – **English accepted** – **Documents mandatory to be in official national language** –

	Applicable national legal framework/ Reference Regulation 14 SI 190/2004
Submission Fees	**Fees for trial submission mandatory** Yes **Fees** Fees published for 2015 are provided below as a guide, but should be checked at time of application: (1) Fees for Clinical Trials involving general medicinal products: - Phase IV: IMP used within terms of MA 269 Euro/IMP used otherwise than in accordance with MA 538 Euro - Phase I,II,III: IMP containing established active substance 538 Euro/IMP containing new active substance 1443 Euro - Notice of amendment: 84 Euro (2) Fees for Clinical Trials involving medicinal products for gene therapy etc. - Phase IV: IMP used within terms of Marketing Authorisation: 538 Euro/IMP used otherwise than in accordance with MA 1076 Euro. - Phase I,II,III: IMP containing established active substance 1076euro/IMP containing new active substance 2889euro - Notice of amendment: 84 Euro - Review of DSUR: 170 Euro - Review of DSUR where HPRA are rapporteur under a work-sharing procedure: 1000 Euro **Waiver for academic (non-commercial) studies possible** Yes **Payment requirements (timelines)** Prior to submission of application **Official guidance on required fees** Fees for applications are laid down in the HPRA (Fees) Regulations, which are made each year by the Minister for Health. Detailed information is available from the HPRA 'Guide to Fees for Human Products', the 'Fee application form for human products' from the HPRA website in section: Medicines>Regulatory Information>Medicines fees. **Applicable national legal framework/ Reference** Fees are mandatory to be paid to the CA for clinical trial authorisation according to Regulation 14 SI 190/2004. **Additional Information** HPRA fee form and proof of payment are required at time of clinical trial application. In circumstances where there is no financial support for the conduct of the clinical trial, the investigator may be entitled to a fee waiver. Any request for a fee waiver should be clearly stated in the cover letter with the clinical trial application.
Timelines Authorisation	**General timespan (max nr days)** 60 **Mode of approval (General)** Explicit (written) **ATMP/GMO trials (max nr days)** 90 NB! The HPRA strongly recommends that the applicant requests a pre-submission meeting to discuss the potential submission in these categories.

Mode of approval (ATMP/GMO trials)

Explicit (written)

External expert advice required (max nr days)

+ 90

Xenogeneic cell therapy (max nr days)

No time limit

Mode of approval (Xenogeneic cell therapy)

–

Timespan counted from

Date of receipt of valid application
(Applications are validated on receipt, and start of the procedure is held pending submission of any additional information)

Additional Information

Ad approval procedure:
Once the application is validated, the application is assesed and wtihin 25 days (30 days ATMPs and GMOs), a written notice is sent setting out either acceptance of the request, with conditions if necessary, or grounds for non-acceptance.
If grounds for non-acceptance are sent, the applicant must respond and submit an amended request within 14 days (30 days - or more if HPRA agrees- for ATMP and GMOs). Following assessment of response, and within 60 days (90 days for ATMP and GMOs) of the receipt of the original valid application, a final written notice of the outcome is sent to the applicant.

Timelines for Authorisation procedures are described in detail in the Guide to Clinical Trial Applications, available on the HPRA website in section: Medicines>Regulatory Information>Clinical trials>Clinical Trial Applications.

Amendments/ Substantial Amendments (SA)

Notification mandatory for

–

Authorisation mandatory for

Any substantial amendments
(as specified in Regulation 21 SI 190/2004)

Responsible for submission of SA

Sponsor

Timeline for approval of SA (max nr days)

35
From date of receipt of valid application

Guidance on submission of SA

The procedure for amendment applications follows the European Commission’s CT-1 guideline, including the process or classification of substantial/non-substantial amendments.

Detailed information on performing national submission for Ireland is provided in the HPRA Guide to Clinical Trial Applications, which is available on the HPRA website in section: Medicines>Regulatory Information>Clinical trials>Clinical Trial Applications.

Applicable national legal framework/ Reference

Regulation 21 & 22 SI 190/2004

Safety Reporting

Responsible for AE reporting to CA

Sponsor

Sponsor must declare reportable events to

National CA
EMA Eudravigilance CT Module (EVCTM)
NB: In parallel to both!

Reportable AEs

SAE (Serious Adverse Event)
SUSAR (Suspected Unexpected Serious Adverse Reaction)

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

As soon as possible
Within a max of 7d upon first knowledge (+ 8d for additional information)

All other SUSARs

As soon as possible
Within a max of 15d upon first knowledge

SAE /SADE must be reported

–

National standard reporting form available

–

Standard Reporting Form

A standard online form for investigator-led trials is available on the HPRA website in section: Medicines > Regulatory Information > Clinical trials > Reporting Serious Adverse Events .

Reporting format - Options

Electronically

Preferred format

–

Annual safety report shall be provided by sponsor to

–

Guidance on AE reporting procedure

SUSAR reporting requirements are in accordance with the ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, CT-3’, and the requirements specified in the HPRA ‘Guide to Electronic Submission of ICSRs and SUSARs Associated with the Use of Human Medicines’ (available on the HPRA website in section: Reporting Serious Adverse Events).

Detailed guidance on the notification of adverse events, submission of DSURs and other safety related events, are described in the HPRA Guide to Clinical Trial Applications, which is available on the HPRA website in section: Medicines>Regulatory Information>Clinical trials>Clinical Trial Applications. The guidance is based on standard EU safety reporting requirements, as described in the European Commission’s guidance CT-3.

Investigator shall report SAE to

Sponsor

Reporting timeline

Immediately

End of Trial	**End of trial declaration mandatory for** All clinical trials requiring authorisation by CA **Responsible for End of trial declaration** Sponsor **Regular Termination - Declaration timespan (max nr days)** 90 **Timespan counted from** – **Early/premature Termination - Declaration timespan (max nr days)** 15 **Reasons for early termination shall be clearly stated** Yes **Standard Declaration form** European "Declaration of the End of Trial Form" to be used. **Guidance on End of trial declaration** The procedure for End of Trial notification follows the EU Commission's CT-1 and CT-3 guidance. Detailed information on performing national submission for Ireland is provided in the HPRA Guide to Clinical Trial Applications, which is available on the HPRA website in section: Medicines>Regulatory Information>Clinical trials>Clinical Trial Applications **Applicable national legal framework/ Reference** Regulation 28 SI 190/2004 **Additional Information** Note: If the trial ends in Ireland before the trial has ended globally, it is recommended that the sponsor notifies the HPRA in writing as justification for no longer submitting amendments or DSURs.

Ethics committee

Contact Details	**Contact Name 1** Recognised ECs (authorized to provide a single opinion for conduct of an IMP clinical trial; n=12 at present) **Web address** http://health.gov.ie/blog/policy/clinical-trials-involving-medicinal-products/ **Additional Information** A list of the Recognised ECs including contact details is provided on the website of the Department of Health in section Clinical Trials involving Medicinal Products. Only ECs recognised by the ECSB (Ethics Committee Supervisory Body/ Minister of Health) are authorised to assess clinical trials on MP. No central EC.
Ethical Review – General	**Submission for Ethical review mandatory for** All clinical trials on Medicinal Products (MP)

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

In parallel
Sequentially (in any order)

Regulatory and ethics bodies involved in approval process

Competent Authority/-ies (CA)
Ethics committee(s)

Single-Centre Studies - Ethical Review

Ethical approval (favourable opinion) to be obtained from

–

Additional Information

The trial application shall be submitted to a Recognised Ethics Committee which has been recognised by the ECSB (Ethics Committe Supervisory Body/Minister of Health) for the whole state, the part of the state or a particular institution or group of institutions in which the Chief Investigator is professionally based.

Multi-Centre Studies - Ethical Review

Ethical approval (favourable opinion) required from

Recognised EC (authorised to issue a single opinion)

Submission of application required to

Recognised EC (authorised to issue a single opinion)

Additional Information

Only one application for an EC's opinion (regardless of the number of trial sites at which the trial is to be conducted) shall be submitted to the relevant EC which has been recognised by the ECSB(Ethics Committe Supervisory Body/Minister of Health) for the whole state, the part of the state or a particular institution or group of institutions in which the Chief investigator is professionally based. (Regulation 12 SI 190/2004)

A Site Specific Assessment (SSA) should be performed at each participating trial site in Ireland. The standard SSA form (Form 3) to be used shall be completed by the Investigator at each site and forwarded to the Chief Investigator. The Chief Investigator should submit all SSAs to the Recognised Ethics Committee. Form 3 is available on the Department of Health website in section: Clinical Trials involving Medicinal Products >Application Forms.

Submission of Application

Responsible for study submission

Chief Investigator

Entitled to study submission

–

Prerequisites for submission / approval

–

Guidance on study submission available

Yes

Guidance on study submission

The 'Guidance on the Application for Recognised Ethics Committee Opinion and the Ethical Review of Clinical Trials on Medicinal Products for Human Use' provides detailed information on the submission of an application. Available on the Department of Health website in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products.

Applicable national legal framework/ Reference

Regulation 12 SI 190/2004

Submission Format	**Format option(s)** – **Preferred format** – **Standard application form** The Standard Application form (Form1) and the related Applicant's checklist on the supporting documentation (Form2) to be used are available from the Department of Health website in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products. The application form must be signed by the Chief Investigator. The application form together with all the necessary supporting documentation should be provided.
Language of Submission	**Language(s) of application** English **Preferred language of application** – **English accepted** – **Documents mandatory to be in official national language** –
Submission Fees	**Fees for Ethical review mandatory** Yes **Fees for Ethical review** The standard fee for an ethical review is, as follows: € 1000.- for each trial application + €150.- for the trial site +€150.- for each additional site Notification of Amendments: €200.- **Official guidance on required fees** The fees are specifed in the Guidance booklet on applications to Recognised Ethics Committees (RECs), available on the website of the Department of Health in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products. **Applicable national legal framework/ Reference** Fees are mandatory according to Regulation 12 SI 190/2004
Timelines Ethical Review	**General timespan for single-centre studies (max nr days)** 60 **General timespan for multi-centre studies (max nr days)** 60 **ATMP/GMO trials (max nr days)** 90 **External expert advice required: Timespan (max nr days)** + 90 **Xenogeneic cell therapy: Timespan (max nr days)** No time limit

	Clock-stop possible if complementary information requested Yes **Timespan counted from** Date of receipt of valid application **Applicable national legal framework/ Reference** Regulation 13 SI 190/2004 **Additional Information** The applicant must provide details of the EC opinion to the HPRA as soon as it is available to ensure that all Irish records are released and published on the EU Clinical Trials Register.
Amendments/ Substantial Amendments (SA)	**Ethical review mandatory for** Any substantial amendments **Responsible for notification of SA** Sponsor **Standard notification form available** Yes **Standard notification form** The standard form to be used (Form 4) is available on the Department of Health website in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products > Application Forms **Timeline Ethical review of SA (max nr days)** 35 From date of receipt of valid application **Guidance on submission of SA** Further details on the submission procedure of amendments are provided in the Guidance booklet on applications to Recognised Ethics Committees (RECs), available on the website of the Department of Health in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products. **Applicable national legal framework/ Reference** Regulation 21 & 22 SI 190/2004
Safety Reporting	**Reportable AEs** SAE (Serious Adverse Event) SUSAR (Suspected Unexpected Serious Adverse Reaction) **Investigator shall report SAE to** Sponsor **Reporting timeline** Immediately **Responsible for AE reporting to relevant EC(s)** Sponsor **SUSAR being life-thereatening or leading to death must be reported** Within a max of 7d upon first knowledge (+ 8d for additional information) **All other SUSAR must be reported** Within a max of 15d upon first knowledge

SAE/SADE must be reported

–

National Standard Reporting form available

No

Standard Reporting Form

Only standard 'Safety Report Cover form' (Form 5) for Annual safety report (available on the website of the Department of Health in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products>Application Forms.

Reporting format - Options

–

Preferred reporting format

–

Provision of Annual safety report mandatory

Yes

Guidance on AE reporting procedure

Details on AE reporting procedures (expedited and annual safety reports) is provided in the Guidance booklet on applications to Recognised Ethics Committees (RECs), are available on the website of the Department of Health in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products

End of Trial

End of trial Declaration mandatory

Yes

Responsible for End of trial Declaration

Sponsor

Regular Termination - Declaration timespan (max nr days)

90

Timespan counted from

Last participant - last visit

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

15

Reasons for early termination shall be clearly stated

Yes

Standard Declaration form

The standard Declaration of the End of a Clinical Trial form (Form 6) applies to both the normal conclusion and premature termination available on the Department of Health website in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products > Application Forms

Guidance on End of trial declaration

Further details on the End of Trial obligations are provided in the Guidance booklet on applications to Recognised Ethics Committees (RECs), available on the website of the Department of Health in section: Policy A-Z>C>Clinical Trials Involving Medicinal Products.

Applicable national legal framework/ Reference

Regulation 28 SI 190/2004

Study specific Requirements

Sponsor	**Sponsor - Definition available in national law** Yes **Sponsor - Definition (pursuant to national law)** Definition pursuant to Regulation 4 SI 190/2004: 'the person who takes on responsibility for the initiation and management (or for arranging the initiation and management) of, and the financing (or arranging the financing) for that clinical trial". The sponsor or legal representative of the sponsor shall be established within the European Community. **Sponsorship mandatory** Yes **Co-Sponsor - Definition available in national law** No **Co-sponsorship allowed - Additional information** There is no provision for Co-Sponsorship at present, however, this will change when the rules of CT Regulation 536/2014 become applicable. For non-commercial multi-centre clinical trials, it is possible to have a local sponsor in addition to an international sponsor. **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** Freely given informed consent shall be obtained from every subject prior to clinical trial participation (pursuant to Regulation 10, Part 2, S.I no. 374 of 2006). Detailed legal requirements are specified in Schedule 1, Conditions and Principles for the Protection of Clinical Trials Subjects, of S.I No. 190 of 2004. **Applicable national legal framework/ Reference** Regulation 10, Part 2, S.I no. 374 of 2006 Schedule 1 (Conditions and Principles for the Protection of Clinical Trials Subjects) of S.I No. 190 of 2004.
Study Participants - Vulnerable Population	**Minors / Children - Studies allowed** Yes Special provisions apply **Specific provision** A minor is defined as a person under the age of 16 years. **Legal framework/Reference (Minors/Children)** Schedule 1, Part 4 SI 190/2004 **Incapacitated persons - Studies allowed** Yes Special provisions apply **Legal framework / Reference (Incapacitated persons)** Schedule 1, Part 5 SI 190/2004

Emergency situations - Studies allowed

No explicit provisions in national legislation

Specific provisions

Studies including subjects in emergency situations are not explicitly mentioned in Irish legislation. However, clinical studies with incapacitated persons, who are unable by virtue of physical or mental incapacity to give informed consent, are possible under special provisions according to Schedule 1, Part 5 SI 190/2004.

Emergency situation without prior consent of patient or proxy - Studies allowed

–

Pregnant or breastfeeding women - Studies allowed

No explicit provisions in national legislation

Specific provisions

There are no specific provisions in national legislation. Ethics Committees should be clearly informed if pregnant or lactating women are proposed to be recruited to a study.

Data Protection

Notification to DP Authority/ Ombudsmann is mandatory

No

Approval/ authorisation required

No

Specific notification timelines before operations start

–

Language of notification

–

Notification format

–

Data Protection Authority/ Agency - Contact Details

Office of the Data Protection Commissioner

Web address

http://www.dataprotection.ie/

Country

Ireland (IE)

Additional Information

Contact details are available from the website.

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
Other legislation covering DP related issues

National DP act

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. (Part 2 (para 14) S.I 374/2006)

Insurance	**Liability insurance or alternative arrangements for damages mandatory for** Investigator(s) Sponsor **Responsible for covering insurance** Sponsor **Additional Information** The Ethics Committee consider insurance and indemnity during the clinical trial application assessment. Investigators and their clinical staff are covered under the states Clinical Indemnity Scheme. Private hospitals are not covered, with the exception of special arrangements that may in place for a limited number of institutions. The 'Clinical Trial Indemnity Form' (25 October 2013) should also be completed between the sponsor, the hospital and authority and the Investigator. The standard form is available from the website of the State Claims Agency in section: Resources. Further information on the scheme is available on the website.
Quality Assurance/ Quality Control (QA/QC)	**Monitoring** Compulsory **Audit by sponsor** Compulsory **Standard Operating Procedures (SOPs)** Compulsory **Additional Information** Requirements for Quality Assurance/Quality Control, Monitoring and SOPs are as described in EU legislation and guidance and ICH GCP E6.

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)
Clinical Trials on IMPs in Humans	**Applicable national regulations** –

	Transposition of (CT) Directive 2001/20/EC (or comparable national legal framework) EU Directives have been transposed into the Irish Statute Book as the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 to 2009, comprised of: - The European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 to 2009, transposing (A) the EU Directive (S.I No. 190 of 2004), (B) the GCP Directive (S.I No. 374 of 2006) and (C) giving effect to the ATMP Regulation (S.I No. 1 of 2009). - And, Regulation 16(2) of the Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No. 539 of 2007), - And, Regulation 27 of the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I No. 540 of 2007). **Applicable to ATMP/ GMO trials** Yes **Transposition of (GCP) Directive 2005/28/EC** Incorporated in transposition act(s) of Directive 2001/20/EC **Additional Information** Clinical trials are governed by EU Directives, including the Clinical Trial and GCP Directive, and associated guidance including in particular, the International Conference on Harmonisation Guidance and Eudralex, Volume 10 Notice to Applicants.
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 Other legislation covering DP related issues **National DP act** 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. (Part 2 (para 14) S.I 374/2006)