Medicinal Products for Human Use - ITALY

Competent authority

Contact Details

Contact Name 1

Italian Medicines (Drug) Agency/ Agenzia Italiana del Farmaco (AIFA)

Contact Name 2

Clinical Trial Office/ Ufficio Sperimentazione Clinica of AIFA

Phone

+39 06 5978401

Fax

+39 06 59944142

Email Department

sperimentazione.clinica@aifa.gov.it

Address

Via del Tritone 181

ZIP/City

00187 Rome

Country

Italy (IT)

Web address

http://www.agenziafarmaco.gov.it/en/content/clinical-trials

Additional Information

AIFA is operating on behalf of the:
Ministry of Health/ Ministero della salute
Dipartimento del l'innovazione
Direzione Generale dei Farmaci e Dispositivi Medici
Piazzale dell'Industria 20
00144 Roma
Phone + 39 06 59943809
E-mail: Segr.DGFDM@sanita.it
Websites: http://www.salute.gov.it/
(English version: under construction)

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

Clinical IMP trials
Clinical ATMP trials

CA - Registration/ notification without approval required for

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CA - Submission required to

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	National trial registry - Registration mandatory Yes **National trial registry** All clinical trials have to be registered and submitted to the National Clinical Trials Monitoring Centre Database (Osservatorio – OsSC), the database of the Agenzia Italiana del Farmaco (AIFA). **Additional Information** Since Oct 1st 2014, a new version of OsSC has been activated for new Clinical Trial Applications (CTA) fulfilling the condition that all ECs involved in the clinical study have been certified and are included in the EC national register. To access the OsSC, the sponsor/CRO must register via user ID/password. Instructions regarding registration and use of the database are accessible at AIFA website. The complete list of certified ECs and the instructions for CRO self-certification are accessible at the same URL. The registration of the trial data and documents within the OsSC complies with the Italian and European requirements (EudraCT DB) for Clinical Trial electronic data transmission to the CA.
Submission of Application	**Responsible for study submission** Sponsor **Entitled to study submission** – **Prerequisites for submission** – **Guidance on submission of application** All clinical trials have to be registered and submitted to the National Clinical Trials Monitoring Centre Database (Osservatorio – OsSC), the database of the Agenzia Italiana del Farmaco (AIFA). To access the OsSC, the sponsor/CRO must register via user ID/password. Instructions regarding registration and use of the database are accessible on the AIFA website.
Submission Format	**Format option(s)** Online portal **Preferred format** Online portal **Online portal** National Clinical Trials Monitoring Centre Database (Osservatorio – OsSC), the database of the Agenzia Italiana del Farmaco (AIFA). **Standard application form available** Yes **Standard application form** Application via OsSC **Guidance on submission format** Instructions regarding registration and use of the database are accessible on the AIFA website
Language of Submission	**Language(s) of application** Italian English

	Preferred language of application – **English accepted** Data submission must be in Italian, except for free text core data set, where English language is required **Documents mandatory to be in official national language** –
Submission Fees	**Fees for trial submission mandatory** No **Fees** No fees or small fees depending on the type of trial
Timelines Authorisation	**General timespan (max nr days)** 60 **Mode of approval (General)** Tacit (Silent) **ATMP/GMO trials (max nr days)** 90 **Mode of approval (ATMP/GMO trials)** Not specified **External expert advice required (max nr days)** 180 **Xenogeneic cell therapy (max nr days)** No time limit **Mode of approval (Xenogeneic cell therapy)** Explicit **Timespan counted from** – **Applicable national legal framework/ Reference** Art 9 of Legislative Decree 211/2003 **Additional Information** If reasoned objections are expressed by local Competent Authority, the refusal applies only to the individual health facility concerned; if the competent authority is central, the trial cannot be conducted at any centre. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.
Amendments/ Substantial Amendments (SA)	**Notification mandatory for** – **Authorisation mandatory for** All clinical trials requiring authorisation by CA **Responsible for submission of SA** Sponsor

Timeline for approval of SA (max nr days)

Not specified

Applicable national legal framework/ Reference

Section 10.1 Legislative Decree n. 211/2003

Additional Information

The sponsor shall use the OsSC to notify the CA and the EC(s) concerned of any substantial amendments. Non-substantial amendments only require notification of the EC(s) without approval.

If the EC's opinion is favourable and the CA has raised no grounds for non-acceptance, the sponsor may implement the amendment.

Safety Reporting

Responsible for AE reporting to CA

Sponsor

Sponsor must declare reportable events to

Competent Authority
All investigators

Reportable AEs

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

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 SUSARs

Within a max of 15d upon first knowledge

SAE /SADE must be reported

–

National standard reporting form available

No

Reporting format - Options

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Preferred format

Online portal

Online Safety Reporting Portal

Sponsors, or delegated Contract Research Organizations (CROs), are required to send SUSARs only to the EudraVigilance Clinical Trial Module (EVCTM)., following the
"Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)"

Provision of Annual safety report mandatory

Yes

Annual safety report shall be provided by sponsor to

National CA

Applicable national legal framework/ Reference

16 and 17 Legislative Decree n. 211/2003

Investigator shall report SAE to

–

Reporting timeline

–

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 available

No

Standard Declaration form

Use of the online portal OsSC!

National legal framework in place

Yes

Applicable national legal framework/ Reference

Section 10.2 Legislative Decree n. 211

Additional Information

End of the trial shall be declared to the Ministry of Health, the other CAs and the ECs concerned.

Additional Information & Specifics	**Additional Information** Practically, the local CA performs the administrative evaluation of the financial agreement and usually delegates the complete scientific assessment of the trial to the EC of its facility. The central CA (AIFA) performs only a marginal assessment of all the clinical trials employing therapies which do not fall within its competence involving only a check of the data before transmission to EudraCT database and a check of suspected serious adverse reactions (SUSARs). The assessment of the complete clinical trial application and documents is performed by certified ECs. Article 2 t) of Legislative Decree 211/2003 defines the following competent authority for clinical trial on a medicinal product for human use: 1) Local CA: The General Director or Legal Officer, pursuant to current legislation, of the public health facilities at which the clinical trial is conducted, or equivalent facilities, as defined by decree of the Minister of Health; 2) National CA: The Italian Drug Agency on behalf of the Ministry of Health: a) in the cases referred to in Part A of the Annex to Regulation (EEC) No. 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components. b) in relation to the medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity. 3) The National Institute of Health in the case of the newly instituted drugs referred to in Presidential Decree no. 43 of 21 September 2001 and for phase I trials in general.

Ethics committee

Contact Details	**Contact Name 1** Local Ethics Committees (there are 84 certified ECs in Italy) **Web address** https://www.agenziafarmaco.gov.it/ricclin/en/node/26 **Additional Information** The complete list of certified ECs available via AIFA website.
Ethical Review – General	**Submission for Ethical review mandatory for** Clinical IMP trials Clinical ATMP trials **Submission to CA and EC to be performed in the following order** In parallel **Regulatory and ethics bodies involved in approval process** –
Single-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) to be obtained from** Local EC **Additional Information** The clinical trial must be submitted to the reference EC of the health facility where the trial is conducted.
Multi-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) required from** Lead EC (authorised to issue a single opinion)

	Submission of application required to Lead EC + All concerned local ECs for site-specific assessment **Additional Information** Submission to all reference ECs of the participating clinical sites is required. The single opinion (“Parere Unico”) is provided by the ethics committee of the Italian facility where the coordinating investigator is located (lead EC). The trial may not begin at any site until the said opinion has been issued. The other local ECs involved in the trial may send its comments to the (lead) Ethics Committee of the coordinating centre.
Submission of Application	**Responsible for study submission** Sponsor **Entitled to study submission** – **Prerequisites for submission / approval** – **Guidance on study submission** Detailed guidance on the format and documentation of a clinical trial application to be submitted to by the sponsor to the concerned EC(s) is published in Decreto Ministeriale 21 Dec 2007/ Ministerial Decree 21 December 2007 and is accessible in the OsSC. **Additional Information** The application has to be submitted in parallel to the lead EC and all involved local ECs.
Submission Format	**Format option(s)** Online portal **Preferred format** Online portal **Online portal** OsSC: All clinical trials have to be registered and submitted to the National Clinical Trials Monitoring Centre Database (Osservatorio – OsSC), the database of the Agenzia Italiana del Farmaco (AIFA). Since Oct 1st 2014, a new version of OsSC has been activated for new Clinical Trial Applications (CTA) fulfilling the condition that all ECs involved in the clinical study have been certified and are included in the EC national register. To access the OsSC, the sponsor/CRO must register via user ID/password. Instructions regarding registration and use of the database are accessible at the AIFA website. **Standard application form available** No **Standard application form** Use of Online Portal (OsSC)
Language of Submission	**Language(s) of application** Italian **Preferred language of application** –

	English accepted Not specified **Documents mandatory to be in official national language** –
Submission Fees	**Fees for Ethical review mandatory** Yes **Waiver for academic (non-commercial) studies possible** Yes **Fees for Ethical review** € 1500,- to 4000, (usually for profit trials only)
Timelines Ethical Review	**General timespan for single-centre studies (max nr days)** 60 **General timespan for multi-centre studies (max nr days)** 60 (30 days Lead EC + 30 for local ECs of collaborating centers) **ATMP/GMO trials (max nr days)** 90 **External expert advice required: Timespan (max nr days)** 180 **Xenogeneic cell therapy: Timespan (max nr days)** No time limit **Clock-stop possible if complementary information requested** Yes **Timespan counted from** Date of submission of valid application **Applicable national legal framework/ Reference** Section 6.3-5 Legislative Decree n. 211(Single-centre trials) Section 7 Legislative Decree n. 211 (Multi-centre trials) **Additional Information** Ad Mulit-centre trials: The single opinion has to be expressed within 30 days from the date of receipt of a valid application; the ECs of the participating sites may send its comments to the EC issuing the single opinion. The final single vote shall be notified to the sponsor, the other ECs involved and the Ministry of Health. The extension time spans applicable for single-centre trials (e.g.: + 30 days in case of advanced therapies) also apply to the EC expressing the single opinion. Within a maximum of further 30 days from the date of receipt of the single opinion, the ECs of the collaborating centres shall notify the sponsor, the other committees and the CA of their acceptance or rejection of the single vote.
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

Submission via OsSC online portal.

Timeline Ethical review of SA (max nr days)

35 (single opinion within 20 days by lead EC + acceptance or rejection within further 15 days by local ECs)

Applicable national legal framework/ Reference

Section 10.1 Legislative Decree n. 211

Additional Information

Non-substantial amendments only require notification of the EC(s) without approval.
If the EC's opinion is favourable and the CA has raised no grounds for non-acceptance, the sponsor may implement the amendment.

Safety Reporting

Reportable AEs

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

Investigator shall report SAE to

Sponsor

Reporting timeline

Immediately (without delay)

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

–

Sponsor is obliged to notify all investigators of SAE/ SADE occurrence

Yes

National Standard Reporting form available

–

Reporting format - Options

–

Preferred reporting format

–

Provision of Annual safety report mandatory

Yes

Applicable national legal framework/ Reference

Section 16 and 17 Legislative Decree n. 211

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** – **Early/premature Termination - Declaration timespan (max nr days)** 15 **Reasons for early termination shall be clearly stated** Yes **Applicable national legal framework/ Reference** Section 10.2 Legislative Decree n. 211

Study specific Requirements

Sponsor	**Sponsor - Definition available in national law** Yes **Sponsor - Definition (pursuant to national law)** Trial Sponsor: an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of the the clinical trial (Art 2 Legislative Decree 211/2003) **Sponsorship mandatory** Yes **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 **Additional Information** The sponsor or a legal representative must be established in the EU (pursuant to Section 20 Legislative Decree 211/2003).
Study Participants - Informed Consent (IC)	**Standard IC form (ICF) available** Not specified **IC is regulated by law** Yes

Informed Consent - Definition/ Requirements

Informed Consent is specified in Section 2-5 of Legislative Decree n. 211:
It is the decision to take part in a clinical trial which must be written, dated and signed, taken freely after being duly informed of its nature, significance, implication, risks and right to revoke any time without detriment to the subject.
If the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases. When the person is not capable of giving consent, the informed consent can be obtained by his or her legal representative if the subject's presumed will is represented.

For genetic or genotype/phenotype studies a specific informed consent is required and the aim of the study should be stated when the informed consent is obtained. If the stored material is later used for other purpose than the originally stated ones, a new informed consent should be obtained again from the participants.

Study Participants - Vulnerable Population

Minors / Children - Studies allowed

Yes
Special provisions apply

Legal framework/Reference (Minors/Children)

Section 4 of Legislative Decree n. 211

Incapacitated persons - Studies allowed

Yes
Special provisions apply

Legal framework / Reference (Incapacitated persons)

Section 5 of Legislative Decree n. 211

Emergency situations - Studies allowed

No national legal framework available

Specific provisions

The involvement of subjects in emergency situations in a clinical trial is not explicitly mentioned in Italian law (see sections on vulnerable persons in Legislative Decree n. 211)

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

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Conditions allowing trial participation in emergency setting without prior consent

In Italy studies can be conducted, in the absence of a legal representative, provided that:
1.The clinical trial has been approved by a National, independent EC created ad hoc for the study and including scientific, legal and ethic experts and patient representatives
2.the patient has never expressed a negative will to participation in a clinical trial
3. the investigators commit themselves to obtain patient consent whenever (and if) the patient comes back to a conscious state

NB: Despite this recommendation issued in 2012 by the Consiglio Nazionale di Bioetica, in most cases Investigators are reluctant to participate in clinical studies involving unconscious patients incapacitated to provide their consent because court involvement may be needed in many cases.

Pregnant or breastfeeding women - Studies allowed

No national legal framework available

Specific provisions

The involvement of pregnant or lactating women in a clinical trial is not explicitly regulated in Italian law (see sections on vulnerable persons in Legislative Decree n. 211).

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

Italian Data Protection Authority DPA - Garante per la Protezione dei Dati Personali

Phone

+39 06 6967 71

Fax

+39 06 6967 73785

E-Mail

rp@gpdp.it

Web address

http://www.garanteprivacy.it

Address

Piazza di Monte Citorio, 121

ZIP/City

00186 Rome

Additional Information

The rights of the subject to physical and mental integrity, to privacy ant to the protection to the personal date are regulated and safeguarded by the Data Protection Code - Legislative Decree no. 196/2003, superseding the Data Protection Act 1996 (Statute no. 675 of 31 Dec 1996).

Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)

–

Insurance

Liability insurance or alternative arrangements for damages mandatory for

Investigator(s)
Sponsor
Study participants

Responsible for covering insurance

Sponsor

Additional Information

Insurance is required for all clinical trials in Italy in order to protect trial subjects and cover the third-party liability of the investigator and the sponsors in the event of claims form damages by trial subjects.
If the sponsor is a public body the cost of the insurance shall be covered by the budget allocated to it. (Section 3.1f9 and 3.4 Legislative Decree n. 211).

NB: For non-commercial clinical trials (ie, not sponsored by for profit enterprises) the general insurance contract of the hospital of the participant can cover the participant (according to a specific decree on non-for-profit trials).
However, the specific ministerial decree released on insurance does not distinguish commercial and non-commercial trials. Thus, in some cases the EC could require a specific insurance also for a non-commercial trial. It just a matter of different interpretation of two laws.

Quality Assurance/ Quality Control (QA/QC)

Monitoring

Compulsory

Audit by sponsor

Compulsory

Standard Operating Procedures (SOPs)

Compulsory

National legislation

General Information: Applicable Legislation & Conventions

Official website providing relevant national legislation available

Yes

Official website providing relevant national legislation

A collection of national regulations about clinical trials with medicines) is provided on the website of the AIFA portal of Clinical Research with Medicines in section Regulations.

Clinical Trials on IMPs in Humans

Applicable national regulations

Transposition of (CT) Directive 2001/20/EC
Other

Transposition of (CT) Directive 2001/20/EC (or comparable national legal framework)

Legislative Decree n. 211 of 24 June 2003 / Decreto legislativo n. 211.
Available in Italian and English (unofficial translation)

Transposition of (GCP) Directive 2005/28/EC

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Other applicable regulations/ implementing provisions (Acts, laws, decrees, ordinances, circulars, etc)

(1) Decreto Ministeriale 21 Dec 2007 (it)/ Ministerial Decree 21 December 2007 (en_non official translate): As stated in Article 3 of this Decree, the local CA (section 1) may, completely or partially, appoint the EC concerned to the assessment of documentation as of attachment 1 to this decree; anyway, the application form, properly filled in compliance with appendix 5 to this decree, must be always forwarded to the Competent Authority.

(2) Decreto Ministeriale 12 Maggio 2006/ Ministerial Decree 12 May 2006 (only available in Italian): This decree regulates the responsibility and role of the independent ECs.

	Additional Information ad: Legislative decree 211/2003: The Decree issues additional provisions in order to better regulate the responsibility and the role of the ECs and to give instructions a.and to give instructions about the type of information to be submitted through the national database.
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 Implementing Decrees and Ordinances **National DP act** Legislative Decree no. 196 of 30 June 2003 (Italian Personal Data Protection Code), superseding the Data Protection Act 1996 (Statute no. 675 of 31 Dec 1996)

Definition

IMP/IMP Study	**IMP - Definition available in national law** Yes **IMP - Definition** Definition of IMP is provided in Art 2 (1.d) of Legislative Decree 211/2003. The investigational medicinal product is the study drug and the comparator including the placebo or active drug. The drugs which are not the direct subject of the experimental design, but their use is considered in the protocol, are also considered investigational medicinal products: 1. Drugs with market authorisation, used according to the indications, included in the protocol as needed to the success of the trial, such as drugs to prevent or treat side effects of the investigational medicinal product. 2. Drugs with market authorisation, used outside the approved indication. 3. Drugs without market authorisation, but with market authorisation in other countries of the EC, used within or without the approved indication. 4. Challenge agents, i.e., drugs that are used to induce physiological reactions needed to evaluate the effect of the investigational medicinal product. The rescue drug, and background treatments are not investigational medicinal products.