CALL AIFA 2018
FOR INDEPENDENT RESEARCH ON MEDICINAL PRODUCTS
ITALIAN MEDICINES AGENCY

Allocation of funding for independent research on medicinal products pursuant to article 48, paragraph 5, letter g), and paragraph 19, letter b), number 3, of Decree-Law 30 September 2003, No. 269, converted into Law 24 November 2003, No. 326 and subsequent modifications and additions.

PREAMBLE

The Italian Medicines Agency, hereinafter referred to as AIFA, in the context of promoting independent research on medicinal products, funded pursuant to art. 48, paragraph 5, letter g), and paragraph 19, letter b), number 3, of Decree-Law 30 September 2003, No. 269, converted into Law 24 November 2003, No. 326, intends to promote research aimed at generating new evidence, with potential effects on the Italian Health Service.

The main purpose of this Call is to encourage research on issues consistent with the aims and objectives of the National Health Service (NHS), by financing studies of significant interest for the health of citizens, also taking into consideration the potential effects on the regulatory activity of AIFA.

The regulation of non-profit research is to be found in the Decree of the Minister of Health 17 December 2004, on *"General requirements and conditions, relating to the execution of clinical trials of medicinal products, with particular reference to those for the purpose of improving clinical practice, as an integral part of health care"*.

The amounts allocated to the activity of this Call derive from the Fund referred to in art. 48, paragraph 19, letter b) for the year 2018, approved by resolution of the Board of Directors 29 November 2018, No. 32, as resulting from the Agency's budget documents for a total of euro six million five hundred thousand (6,500,000.00).

GENERAL PART

DEFINITIONS

The terms listed below, contained in this Call, meet the following definitions:

- **Principal Investigator or Coordinator of the research project**: scientific manager and applicant for the Research Project for the AIFA Call for independent research on medicinal products;
- **Clinical Trial or Clinical Study:** any investigation in human subjects intended to identify or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) being tested; and/or identify any adverse reactions to a medicinal product(s) being tested; and/or to study the absorption, distribution, metabolism and excretion of a medicinal product(s) being tested with the object of assessing its (their) safety and/or efficacy;
- **Observational study or non-interventional trial:** any study where medicinal products are prescribed in accordance with the terms of the marketing authorization (AIC). The assignment of the patient to a specific therapeutic strategy is not decided in advance by a trial protocol, but falls within current practice and the decision to prescribe the medicinal product is completely independent of that of including the patient in the study. No additional diagnostic or monitoring procedures should be applied to the patients and, and epidemiological methods should be used for the analysis of collected data, according to the provisions of AIFA Determination 20 March 2008 on *"Guidelines for classification and conducting observational studies on medicinal products"* published in the OJ 31 March 2008 No. 76;
- **Meta-analysis:** clinical-statistical technique of analysis of the literature related to interventional or observational studies that allows a qualitative assessment by examining the validity of a study and a quantitative one to express the overall estimates through the combination of the results of the single studies;
- **Protocol form:** application form to be filled in electronically, in accordance with Annex 1 of this Call, at the time of submission of the Research Project;

- **Operating Unit:** centre involved in the Research Project, well defined from the functional point of view within the structure it belongs to (laboratory, division, clinical department, diagnostic department), which operates in the research project according to a specific activity clearly stated in the protocol.

THEMATIC AREAS

The Research Project must be referred to one of the thematic areas identified below and to one of the relevant lines of research, where specifically indicated.

The identification of the thematic area and line of research is mandatory and the Principal Investigator is responsible for selecting the most appropriate one in the protocol form.

1) Rare diseases

2) Comparative controlled clinical studies

3) Chimeric Antigen Receptor T-cell (CAR-T cells)

Thematic area 1 – Rare diseases.

Clinical studies on rare diseases may be aimed at answering any question related to this area, for which it is believed that the study project can contribute to increase currently available evidence, with the ultimate goal of identifying therapeutic strategies. The priority for projects in this area should be the capacity to generate evidence with tangible outcomes for the populations, the concerned pathologies, the National Health Service, as well as the research methodology in such area and the identification of endpoints clearly relevant for patients.

All potentially lethal or very serious diseases, with a prevalence of less than 5 cases per 10,000 people in the European Union (EC Regulation No. 141/2000) are defined as "*rare diseases*".

To identify them, it is possible to refer to the list of rare diseases available on the institutional website of the Ministry of Health http://www.salute.gov.it/BancheDati/anagrafi/MRR (Decree of the Ministry of Health No. 279 18 May 2001 and Decree of the President of the Council of Ministers 12 January 2017), to the list of the National Institutes of Health (NIH) available at the link https://rarediseases.info.nih.gov/ or to the list of the website for rare diseases and orphan drugs (Orphanet) available at the link https://www.orpha.net/consor/cgi-bin/Disease.php?lng=IT .

Studies on rare tumours are not allowed in the aforementioned thematic area.

Phase I and II studies may be submitted in this thematic area.

The rare diseases topic must be declined according to at least one of the following lines of research, also integrating several lines of research in the same Project:

- studies aimed at prevention and management from frailty to disability in rare diseases;
- confirmatory studies on well-established medicinal use in rare diseases;
- studies on new therapeutic strategies for rare diseases, including advanced therapy medicines;
- confirmatory studies (phase II/III) on low-cost medicinal products that have passed the pre-clinical and clinical study phases I/II, as a therapeutic alternative to high-cost medicinal products already marketed for the treatment of rare diseases;
- comparative controlled clinical studies between orphan drugs and drug products currently used in clinical practice, particularly on rare neurodegenerative diseases;
- clinical studies on rare diseases caused by enzyme defects;
- clinical efficacy studies on medicinal products approved for treatment of rare diseases through conditional approval or based on modest evidence;
- clinical studies in paediatric population.

Thematic area 2 - Head to head clinical trials

This thematic area intends to promote the realization of studies aimed at providing information on the comparative efficacy and/or safety of specific medicinal products (or their classes) for pathologies with high epidemiological-clinical and care relevance.

It arises from the need to obtain new comparative evidence within therapeutic classes with a high expenditure impact on the NHS and for which, in some cases, there are no direct comparisons.

The purpose of the studies in this area is also to define the potential overlapping of some treatments on a more robust scientific basis.

For this area must be submitted only randomized and controlled phase III or IV studies.

This thematic area must be declined according to at least one of the following lines of research, also integrating several lines of research in the same project:

- head to head comparison clinical trials between plasma-derived and recombinant factor VIII in prophylaxis of bleeding episodes in patients with Hemophilia A;
- head to head comparison clinical trials within dipeptidyl-peptidase-4 inhibitors (DPP4i), glucagon-like peptide-1 analogues (GLP1a) and type 2 sodium-glucose transporter inhibitors (SGLT2) drug classes;
- head to head comparison clinical trials between monoclonal antibodies in the onco-hematologic area for overlapping therapeutic indications;
- head to head comparison clinical trials within anti-TNF-alpha and anti-interleukine drug classes for immunosuppressive therapies for overlapping therapeutic indications;

- head to head comparison clinical trials on biosimilars of monoclonal antibodies, with particular reference to the investigation of the effect of the therapeutic switch.

Thematic area 3 - Chimeric Antigen Receptor T-cell (CAR-T cells)

Immunotherapy and the ability of genetic engineering to induce T-cell response specificity against tumour cells have enabled a revolutionary therapeutic approach in the treatment of cancers for which standard traditional therapies have not proved to be effective.

CAR-T cell therapies have shown high response rates in relapsed or chemically refractory B-cell cancers, such as non-Hodgkin B-cell lymphoma (LNH) and acute lymphoblastic leukemia (ALL), with high remission rates and long-term effect. CAR-Ts could also be applied in the treatment of solid cancers, although many critical issues have been found in this area. In fact, compared to hematological malignancies, the "targeting" has additional difficulties due to the genetic instability of the tumour cells, the histopathological characteristics of the tumour, the inadequate "trafficking" of CAR-T cells in the tumour sites and the heterogeneity of the tumours. The clinical success of CAR-Ts is partly limited by a complex profile of adverse events, in some cases even fatal, including mainly neurotoxicity and cytokine release syndrome, the latter caused by the massive release of cytokines (CRS) from the tumour cells or from the autoimmune activity that is triggered in healthy tissues expressing the target antigen.

To date, the safety profile of CAR-T needs to be fully characterized and long-term safety and the risk of secondary cancers still need to be defined. Furthermore, with the increase of the number of treated patients and of the follow-up duration, the first data on refractoriness and recurrence of the disease are being recorded, whose underlying mechanisms have yet to be clarified.

The studies submitted in this area should be focused on the issues - still open - concerning the safety and efficacy of the treatment and the optimal positioning of CAR-T with respect to traditional treatments, also in order to expand its clinical application.

There are no specific lines of research for this thematic area, but compliance with the following general principles is requested:

- the cell factories must be authorized by AIFA for the production of products for gene therapy at the time of the submission of the Research Project for this Call;
- the applicant must have prepared the dossier of the product for the gene therapy under study at the time of submission;
- only clinical studies evaluating the benefit/risk ratio of CAR-T are admitted, aimed at a preliminary assessment of potential efficacy and adverse effects are allowed;
- phase I and phase II studies are admitted;

- studies in oncology can concern both hematological and solid tumours;
- proposals that include the optimization of clinical trials design are also admissible, to allow early assessments of safety and/or efficacy and, therefore, the identification of responsive patients, also through pharmacogenomic evaluations;
- clinical studies must accurately describe the section related to the assessment of treatment safety with reference to neurotoxicity, serious adverse events (such as, for example, cytokine release syndrome after treatment), haematological events. In particular, with reference to acute toxicity, the studies have to include monitoring of the nature of the related toxicity and the severity of the reaction as well as the strategies for mitigating/managing adverse events;
- studies aimed at identifying the predictive factors of response or toxicity;
- studies aimed at analyzing disease's non-response or recurrence mechanisms;
- studies aimed at characterizing post-treatment clinical history;
- clinical studies aimed at optimizing the therapeutic process.

GENERAL REQUIREMENTS

Types of Research Projects

The submission of interventional clinical studies, observational studies and meta-analysis is allowed.

At the time of the submission of the Research Project, the studies must not have already been submitted to the Competent Authority (CA) and/or the Ethics Committee (EC).
If the Research Project is submitted to the CA and/or the EC in the period between submission deadline of this Call and the publication of the evaluation results on AIFA institutional website, the Principal Investigator is required to promptly give communication of that to the Independent Research Office of AIFA.

Since the assignment of the funding for Independent Research Calls aims at carrying out research on the use of medicinal products and, in particular, on comparative clinical trials of medicinal products, with the aim of demonstrating the added therapeutic value, as well as on orphan and life-saving medicinal products, only pharmacological studies are allowed.
With regard to interventional studies, they should be Phase III and IV, unless otherwise indicated in the thematic areas or in the specific lines of research.

Trial Design

Only Research Projects with a single trial design are allowed. Projects whose realization depends on preparatory results to be achieved in studies not yet completed are not eligible.

Multicentre Studies

In case of multicentric Research Projects, the coordinating centre and the participating clinical centres must be exclusively national. International multicentre studies are not allowed.

Duration of the Projects

Observational and interventional studies lasting more than thirty-six (36) months are not allowed.

The expected duration for the realization of the study as expressly indicated in the study protocol can be extended of a further period of a maximum six (6) months in order to allow the processing of data and the presentation of the Final Study Report.

In case of meta-analysis, the maximum duration of the study project must not exceed twelve (12) months, including the presentation of the Final Study report.

Requirements for the Applicant Institution

The Applicant Institution must be a structure or body or public institution or equivalent to it or foundation or moral, research and/or health body or scientific society/association or research society not for profit or Institute of hospitalization and care with scientific character (IRCCS), as required by art. 1, paragraph 2, letter a) of Ministerial Decree 17 December 2004.

The Applicant Institution must not be the patent holder of the medicinal product being tested or its marketing authorization holder (AIC) and must not have economic co-interests with the manufacturer of the medicinal product being tested.

At the time of the submission of the Project, a declaration signed by the legal representative of the Applicant Institution attesting the non-profit nature of the Institution must be attached.

For IRCCS of private nature, the Project must be accompanied by a declaration from the legal representative attesting that the experimentation takes place in the context of activities for which they have obtained their recognition as IRCCS by the Ministry of Health.

Requirements for the Principal Investigator

The Principal Investigator is the scientific responsible and has the task of submitting the Research Project to AIFA for the purposes of the funding foreseen in this Call for Independent Research on Medicinal Products.

For a clinical trial, the Principal Investigator should be a physician or dentist qualified for the purpose of the trial. He will be responsible for study coordinating and conducting and he will have the obligations provided for by current legislation.

For projects involving more than one Operating Unit, the Principal Investigator will also be the study coordinator.

The Principal Investigator must:

- submit only one Research Project;
- not have received funding for projects submitted in the 2012, 2016 and 2017 AIFA Calls;
- have a permanent employment within his/her institution for the duration of the submitted project. Subjects who have reached retirement age and/or who are close to retirement in the years of study conduction cannot apply as Principal Investigator;
- have the position and the competences of a promoter-investigator as envisaged by the national law on clinical trials, once the proposed Research Project is selected;
- have the agreement with his or her institution and submit it at the time of the application along with the protocol form;
- have a deep knowledge of the national legislation on clinical research, including non-profit research, for a correct implementation during the study authorization and conduction;
- not be the patent holder of the medicinal product being tested or the marketing authorization holder (AIC) and not have economic co-interests with the manufacturer of the medicinal product being tested.

Number of submitted projects and operating units

The Principal Investigator can submit only one project; the Operating Unit of the Principal Investigator can participate in up to three projects as a coordinating centre.

For multidisciplinary University Departments it is possible to submit a project for each clinical area in the department.

The name and the functions of participating Operating Units must be clearly stated in the protocol form.

The Principal Investigator must declare the recruitment capacity of each Operating Unit, indicating the number of patients with the medical condition object of the Study followed in the last year.

FUNDING OF PROJECTS: MAXIMUM CEILING AND ITEMS ELIGIBLE FOR FUNDING

The maximum amount that can be funded for each project is one million five hundred thousand euros (1,500,000.00) for interventional studies, five hundred thousand euros (500,000.00) for observational studies and seventy-five thousand euros (75,000.00) for the meta-analysis.

Research Projects whose budgets exceed the amounts indicated above are not permitted.

The expenditure items that can be funded with this AIFA Call and the procedures for filling in the budget section are indicated in Appendix B "Guidelines for allocation of budget expenditures".

As required by the aforementioned Ministerial Decree 17 December 2004, the costs for medicinal products with a market authorization that are used according to this authorization and which are charged to the NHS, remain to be charged to the NHS.

In the case of a use not according to the marketing authorization (AIC), the medicinal products cannot be charged to the NHS.

Medicinal products used pursuant to Law No. 648/96, cannot be charged to the NHS when they are used in a Clinical Trial, even if the trial is funded by AIFA; therefore, the relative costs are charged to the investigation.

Co-funded projects

There is the possibility of co-financing by public or private companies or bodies with an interest in supporting the independent research program of AIFA. In particular, co-financing by private companies is allowed only in the following ways:

a) medicinal products reimbursed by the NHS can be provided in the case of a packaging for a “blind” administration;
b) medicinal products used for indications other than those authorized can be supplied;
c) public bodies and non-profit organizations and/or associations can also co-finance individual Studies; the declaration of availability for co-financing must be submitted within the protocols submission deadline.

If the costs for the medicinal product (points a and b) are covered by a pharmaceutical company, a written commitment must be obtained from the company. This declaration must be included in the documentation attached to the application form ("budget" section) together with study protocol submission.

The co-financings obtained after the submission of the Research Project must be promptly communicated to AIFA Independent Research Office which will verify its admissibility and

proceed to request an equivalent reduction of the initially proposed budget, before the contract signature.

PROJECT SUBMISSION PROCEDURES

The protocols must be submitted exclusively by telematic means through the link http://aifa.cbim.it, no later than 30 July 2019 at 06.00 PM.

The date/time of electronic submission of the application for participation in this Call is attested by the IT application that will issue a specific receipt.

For the Project submission it is necessary that the Principal Investigator carries out the accreditation to the system in advance and accesses to it. The person requesting the accreditation must be the Principal Investigator. Projects in which the Principal Investigator is a person different from the one who performed the accreditation will not be accepted.

Projects submitted in ways other than those described above or sent after the abovementioned deadline or where mandatory fields are not properly filled in will not be accepted for evaluation.

The Project has to be written in English, according to the electronic protocol form (See "Guidelines for the compilation of the Protocol Form" - Annex 1 and "Guidelines for allocation of budget expenditures" - Appendix B).

Online guide for the compilation of the Protocol Form is available.

For a correct compilation and submission of the Protocol Form, please note that the system is optimized for Google Chrome on Windows and that PDFs need to be managed with Adobe Acrobat Reader.

PROCESSING OF PERSONAL DATA

Personal data shall be processed exclusively for the purposes indicated in this Call and in compliance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council 27 April 2016, as well as the provisions of Legislative Decree 30 June 2003, No. 196, as amended by Legislative Decree 10 August 2018, No. 101.

VALIDATION OF PROJECTS BY AIFA

The projects submitted in accordance with the terms laid down in section "PROJECT SUBMISSION PROCEDURES" are subjected to a validation phase by the Independent Research Office of AIFA aimed at verifying compliance with the requirements of this Call.

Projects which fail validation will not be admitted to the next evaluation phase by international reviewers.

Exclusion from the next assessment phase will be formally communicated to the Principal Investigator.

The exclusion criteria from the Call are listed below:

- submission after expiry of the deadlines indicated and/or using methods other than those provided for in the section "PROJECT SUBMISSION PROCEDURES";
- submission of the Project by a person other than the Principal Investigator;
- submission of more than one Project by the Principal Investigator;
- submission of a Project by a Principal Investigator already successful in the previous Calls for Proposals 2012, 2016 and 2017;
- submission and/or authorization by Ethics Committees and/or Competent Authority;
- Study projects that are not relevant to the area and/or to the line of research of the Call;
- projects that include several trial designs;
- study duration exceeding that foreseen by the Call;
- submission of a project comparable to one of the projects already funded with previous AIFA Calls (list available at the following link http://www.aifa.gov.it/content/archivio-bandi-aifa-ricerca-indipendente-2005-2017);
- co-financing not compliant with the requirements in the paragraph "Co-funded projects";
- absence of the declarations required for submission: agreement between Principal Investigator and his/her institution, agreement between Principal Investigator and Operating Units, declarations in accordance with the provisions of the paragraph "Requirements of the Proposing Institution" and the paragraph "Co-funded projects".

EVALUATION METHOD

Evaluation by international reviewers

All projects which pass the validation phase will be admitted for evaluation by international reviewers.

The evaluation will be carried out by international reviewers, using an IT workflow that allows a match protocols-reviewers based on the specific issues and their expertise. Each Project shall be evaluated by two reviewers who shall assign a score on the basis of criteria defined in Annex 2 containing "Guidelines for the evaluation of study protocols".
The reviewer shall assign to each project a numerical score (from 1 to 9; 1 = outstanding, 9 = poor) along with a judgment, as provided for in Annex 2.
After the individual assessment, the two reviewers shall have a discussion in a specific forum in order to give the project a single score. Studies that at the end of this phase obtain a unique confirmed score higher than 21 are not admitted to the next evaluation phase by the Study Session.
In the event of disagreement between the reviewers, the project shall maintain the double score and shall be subjected to specific evaluation during the Study Session.

Evaluation by the Study Session Commission

The Commission shall be made up of experts appointed by AIFA and selected on the basis of their expertise. As part of the plenary debate, the Commission shall perform the following tasks:

- express an evaluation of any projects for which the international reviewers have not reached an agreement;
- assess the potential effects of the projects on the NHS;
- assess the adequacy of the requested budget;
- define the final score for each Project;
- draft the final ranking of the projects.

Only projects with a score of less than or equal to **21** – which is considered to be sufficient – are declared eligible for funding.

Projects are funded according to the merit list and until the available resources are exhausted. If the entire amount of resources cannot be allocated, unused residual amounts shall be automatically transferred to the resources for the subsequent AIFA Call for independent research.

With reference to the assessment of the adequacy of the proposed budget, the Study Session Commission – only on the projects defined as eligible – assesses the possible adequacy of the proposed budget. For successful Projects with a budget deemed inadequate as excessive compared to the proposed Study, the Independent Research Office shall subsequently proceed to request its

reduction, applying any criteria or indications provided by the Commission during the Study Session.

In case of equal score, the following priority criteria shall apply:

1. Principal Investigator not successful in previous AIFA Calls.
2. Project with higher score for the criterion assessing the impact on the NHS, as assigned by the Study Session Commission.
3. Youngest Principal Investigator.

The final ranking list drawn up by the Study Session Commission shall be transmitted through the General Management to the AIFA Board of Directors, which shall approve the final ranking of the projects admitted to funding.

The final ranking shall be published on AIFA institutional website and a formal communication shall be sent to successful applicants.

In case of false declarations, in compliance with the provisions of D.P.R. 28 December 2000, No. 445, the Principal Investigator shall be held liable pursuant to art. 76 of the same D.P.R. and the Research Project shall be excluded from the ranking even after the conclusion of the evaluation and the funding shall be revoked.

PROJECTS ACCEPTED FOR FINANCING

The legal representative of the Proposing Institution, whose Project Study was successful, shall be called to sign the Contract with AIFA within sixty days of receiving the letter of communication of admission to the financing.

The Principal Investigator have to submit the study documentation necessary for approval to the Ethics Committee and/or AIFA, as Competent Authority, where it is required and within the deadline set in the contract.

If the Principal Investigator of a Project admitted to the financing is no longer in a position to carry out research activities at the awarding Institution (due for example to the termination of employment relationship or for other occurring reasons), the Institution have to nominate a substitute who meets all requirements. In addition to the administrative and regulatory procedures necessary to replace the Principal Investigator of a clinical research, it is necessary to submit to the Independent Research Office of AIFA the necessary documentation consisting of:

- letter of renunciation by the Principal Investigator who proposed the project with adequate motivation;
- authorization to change the Principal Investigator by the institution;
- letter of acceptance by the substitute;
- *Curriculum Vitae* of the incoming Principal Investigator.

AIFA shall proceed with the evaluation of the documentation for the purpose of continuing the funding.

REVOCATION OF FUNDING

AIFA reserves the right to revoke the financing due to serious non-compliance with the contractual provisions or if the Investigation is not conducted in compliance with current legislation on clinical studies.

AIFA also reserves the right to terminate the Contract and revoke the funding in case that the Principal Investigator:

a. for interventional studies, he has omitted to submit an authorization request to AIFA as Competent Authority and/or request for a single opinion to the competent EC of the Coordinating Centre within the dealine indicated in the Contract;
b. for observational studies, he has failed to submit a single opinion request to the EC or failed to notify the EC;
c. has not obtained the authorization by AIFA as competent authority and/or the positive opinion of the EC, as per current legislation;
d. has not sent a request and subsequently obtained the authorization by AIFA as Competent Authority and/or the positive opinion of the EC on protocol amendments necessary for the study prosecution;
e. has not forwarded the reports to AIFA Independent Research Office according to the timing defined in the Contract;
f. has not completed the study within the timing defined in the contract;
g. has not used, as expressly provided for by art. 3, of Law 13 August 2010, No. 136, and subsequent modifications and additions, the bank transfer instrument or other suitable instruments to allow full traceability of the transactions relating to the Contract;
h. has not complied with the amendments submission procedures and has not obtained their authorizations, as required by contract.

The cancellation or revocation of the consent documents by AIFA as competent authority (where required) and/or by coordinating EC, necessary to start and conduct a clinical trial, entails the nullity of the contract and the concomitant revocation of the funding by AIFA.

The termination and dissolution, where foreseen by the contract, shall be communicated by the Independent Research Office through a PEC addressed to the legal representative of the proposing subject.

AIFA also reserves the right to reduce the due funding or to recover the disbursed payments which are not used for the Project, after revision of the economic-financial reports and/or checks at clinical sites, both for interrupted and completed studies.

ATTACHMENTS TO THIS CALL

1. Annex 1 - Guidelines for drafting the Protocol Form
2. Annex 2 - Guidelines for the proposals evaluation
3. Annex 3 – *Fac simile* contracts
4. Appendix A - Study classification
5. Appendix B - Guidelines for the allocation of budget expenditures