CALL 2017

FOR INDEPENDENT RESEARCH INTO MEDICINAL PRODUCTS

ITALIAN MEDICINES AGENCY

Allocation of funding for independent research into medicinal products pursuant to Art. 48, par. 5 lett. g) and par. 19 lett. b), of Decree-Law 30 September 2003, No. 269, converted into Law 24 November 2003, No. 326.

Purpose and general characteristics

The Italian Medicines Agency (henceforth AIFA), in relation to the promotion of independent research into medicinal products, funded in compliance with Art. 48, par. 19, lett. b) of Law No. 326/2003, wants to promote research aimed at gene rating new evidence, with potential spin-offs for the Italian Health System, with special reference to the following areas:

- **Rare diseases;**
- **Paediatric diseases;**
- **Gender medicine;**
- **Safety and efficacy of medicinal products within elderly and ultra-elderly population;**
- **Antimicrobial resistance.**

The proposals submitted within the frame work of AIFA Call 2017 shall be exclusively referred to one of the abovementioned areas as main field of research, based on the indications of the Principal Investigator upon login the application for participation. The possible coexistence of issues of the study project which relate to other areas is allowed; should it add to evidence potentially generated by the study project, it may be considered as a further relevant element of the said project.

The submission is accepted of interventional clinical studies, observational studies as well as studies based on meta-analyses and systematic reviews.

The main goal of independent research on medicinal products funded by AIFA is to generate evidence with a significant impact on the National Health System, on appropriate use of medicinal products, with a view to sustainability for the System, by guaranteeing suitable regulatory consequences of the scientific results;

moreover, the provision will be made to allow for a subsequent study impact re-assessment on health organizational arrangements and on individual clinical practice. To that end, it is a prerequisite that the study projects provide targeted responses in a timeframe showing the existence of such evidence. For this reason only studies not longer than 36 months shall be accepted. As for meta-analyses and systematic reviews, such period shall be limited to 12 months.

The maximum funding ceiling shall amount to 1.500.000,00 euros for each interventional trial, 500.000,00 euros for each non-interventional trial (observational study) and 75.000,00 euros for each meta-analysis or systematic review. In order that the highest number of studies submitted be ensured access to funding, AIFA reserves the right to request a re-modulation of the budget submitted.

In drafting the protocols concerning the five areas selected for the 2017 call, AIFA recommends using the principle of a suitable regulatory outcome of the targeted scientific results. With regard to the protocols submitted, AIFA shall also take into account the following criteria:

- Creation of networks, also between experts of different fields, or starting from big data/registries which allow to establish programs of diagnosis and care, especially for patients with undiagnosed diseases and to streamline research into rare and undiagnosed diseases.
- Innovative approaches with advanced therapies, which contribute to strengthen the Italian cell factory system.
- Innovative character of the study design with reference to methodology and/or statistical issues.
- Identification of alternative strategies to randomised study, allowing a comparable robustness of data generated, also considering the clinical relevance of the results.
- *Ad hoc* statistical designs, by borrowing models typical of rare diseases to study non-rare pathologies, with a view to simplify and facilitate conduct of trials without compromising validity of results.
- Studies on off-label uses for lack of regularly authorised therapeutic alternatives, also limited to the specific population.
- Assessment of adherence to therapy, criticalities in the use of old and new medicinal products (therapy appropriateness).
- Studies using CRISPR technology/iRNA technology.
- Validation of surrogate endpoints/biomarkers (possibly on liquid biopsy and easy to perform).
- *Head to head comparison* of new molecules, also on small populations or through *ad hoc* statistics.
- Comparative studies between sub-populations of patients not included in the registration trials, with special reference to *target therapies* and related expression of *target* genes.
- AIFA/Academia cooperation studies to make use of data included in AIFA monitoring registries.
- Studies aimed at creating network of registries, through merger and realignment of existing Italian registries.

- Studies aimed at assessing use of digital technologies to improve and innovate management processes relating to medicinal products. In particular, studies may concern: analyses of the use of Apps, Wearables and Social Medias in the health field as tools to improve adherence to therapy, to collect safety information or information to assess efficacy; studies on Big Data Analytics to extract and analyze information relating to safety, adherence to therapy or interactions both between medicinal products and between medicinal products and foodstuffs.
- Studies on use and safety of contrast agents in the paediatric population, in pregnant women and in the elderly population.

Below the detailed indications and prerequisites are listed for the independent research projects relating to the five areas selected for the 2017 call.

Thematic areas

Thematic area 1 – Rare diseases.

Clinical studies on rare diseases can be submitted for any study project (relating to rare diseases) which may contribute to improve available evidence aimed at identifying therapeutic strategies. The priority for projects in this area shall be the capacity to generate evidence with tangible outcomes for the populations, the pathologies concerned and on the National Health System, along with the research methodology and the identification of endpoints which are relevant for patients.

Within studies on rare diseases, the presence of vulnerable patients along with issues relating to gender medicine shall be considered factors of further relevance if they improve significance of evidence that can be generated.

A further relevant point for the project shall be the studies of rare diseases which are currently neglected by clinical research, on the basis of information available in public databases on clinical trials.

The rare disease issue shall be applied in the projects submitted according to at least one of the following lines of research, also integrating more lines of research in the same project:

- Studies aimed at identifying the genetic bases of rare diseases currently without diagnosis, in order to steer the related therapeutic strategies**.**
- Creation of public databases with structured and validated data, which may act as historical comparison and control arm in the studies on rare diseases to compensate for shortage of patients to enroll as well as assessment of the evolution of the natural history of the disease, treatment impact on natural history of the disease in real life and evaluation of therapeutic appropriateness in real life.
- Identification of diagnostic biomarkers to find the best therapeutic strategies and to supervise therapy, also as surrogate endpoints, with a view to reducing invasive investigations during the trial

(development of procedures of molecular characterisation, cytogenetics and phenotypical profiles applied to screening, diagnosis, prognostic assessment and monitoring).

- Definition of *ad hoc* statistical models and potential transferability to non-rare pathologies.
- Definition of study designs with proven impact reduction on patient quality of life, without prejudice to robustness of results.
- Clinical studies aimed at examining the transition models from pediatric age to adulthood, with particular reference to care and therapy strategies – also concerning the gender issue; rare diseases and gonadal development.
- Management and prevention of progression from fragility to disability in rare diseases.
- Re-purposing of medicinal products with established use for treatment of rare diseases; new therapeutic strategies.
- Cell therapy studies for rare diseases, especially neurodegenerative diseases; studies on haematopoietic or mesenchymal stem cells for correction of genetic defects or as regenerative therapies.
- Confirmatory studies (phase II/III) on low-cost medicinal products which have passed pre-clinical and clinical study phase I/II, as a therapeutic alternative to high-cost products marketed for treatment of rare diseases. For such studies it is suggested carefully assessing the ratio between trial cost and potential economic impact of the results on the NHS.
- Innovative design of comparison studies between orphan drugs and commonly used medicines in clinical practice.
- Optimisation of posology in rare diseases due to enzyme deficiency.
- Efficacy trials on drugs approved for treatment of rare diseases through *conditional approval* or based on modest evidence.

In order to identify the rare diseases relating to the thematic area in question, reference shall be made to the list of rare diseases by the Istituto Superiore di Sanità (Italian National Health Institute) and to the NIH list of rare diseases.

Thematic area 2 – Paediatric diseases

The exclusion of the paediatric population from clinical trials entails exiguity of efficacy and safety data in such population. The transferability of data obtained from registration trials and from the majority of trials performed globally is influenced by the peculiarity of such population, due to the problems related to development and to the particular pharmacokinetic characteristics.

This can involve that the therapeutic strategies are frequently based on established uses which are not always backed by adequate scientific evidence, so leading to significant deviations in the benefit-risk profiles of medicinal products.

Independent research studies can be the best way to investigate such issues.

The projects dealing with the paediatric population shall include at least one of following lines of research, also integrating more lines of research in the same project:

- Adjustment of doses and frequency of administration to obtain the best benefit/toxicity ratio in the paediatric age.
- Trasfer of information from phase I/II studies on patients resistant to phase II/III randomised paediatric studies, for the upfront assessment also relating to different pathologies or to patients with a high relapse risk.
- Risk assessment studies for off-label therapies in the paediatric population.
- Clinical studies with psychopharmacological drugs in adolescence or pre-adolescence.
- Clinical studies on neurological diseases in the paediatric age.
- Clinical studies on metabolic diseases in the paediatric population.
- Clinical studies with anaesthetics in the paediatric age.
- Clinical studies aimed at improving symptoms and quality of life in patients with autistic spectrum disorders.

Thematic area 3 – Gender medicine

Pharmacological studies show a significant prevalence of male subjects in the population enrolled, mainly (but not only) due to the risks associated with the reproductive age. However, evidence available points out that pharmacodynamics and pharmacokinetics of medicinal products may be substantially influenced by gender, with efficacy and risk profiles in the female sex which do not always correspond with those observed through registration clinical studies. *Real life* studies and targeted studies may contribute to fine-tune the real benefit-risk profile of medicinal products in female population, to explore possible gender-related differences in “dose-response” assessment or to contribute to generate evidence in peculiar conditions of the female gender, which is typically excluded from traditional studies due to potential unknown risks. In this respect, independent research may act as a main integration tool with knowledge generated by profit studies. The projects dealing with the gender medicine issue shall follow at least one of the following lines of research, also integrating more lines of research in the same project:

- Clinical studies on gender-specific risk profile.
- PK and PD studies exploring and underlining the *Drug-Dose Gender Gap.*
- Gender-specific biomarkers, as indicators of therapeutic appropriateness or of response to therapy.
- Clinical studies on autoimmune diseases in pregnancy.
- Drug effect on embryo implantation/successful pregnancy.
- Cardiovascular diseases and gender differences (different efficacy timing of post-ischemic anticoagulant drugs, medicinal products acting on heart re-modeling).
- Obesity and gender differences in pharmacological therapy.

- Implementation of clinical trial models aimed at integrating the PK and PD studies with those of chronobiology, pharmacogenetics and pharmacodynamics, related to the different age brackets, hormonal stages and to critical periods (breastfeeding, pregnancy, menopause, etc.).
- Hepatitis C in women (especially in pregnancy; eradication, prevention of vertical transmission).
- Clinical studies aimed at assessing concomitant user of medicinal products for treatment of particular pathologies (HCV, HIV, epilepsy, some bacterial infections, etc.) and oral/hormonal contraception.
- Assessment of the effects in school age children who were exposed *in utero* to medicinal products (in particular antidepressants, some anticoagulants, etc.): large cohort studies in children exposed and non-exposed *in utero* to specific medicinal products in order to assess potential long-term effects on (neurocognitive) development and growth; research of innovative strategies to evaluate long-term effects (consortia similar to EUROmediCAT).

Thematic area 4 - Safety and efficacy of medicines in elderly and ultra-elderly populations

The exclusion of elderly and ultra-elderly subjects from clinical trials entails a limited availability of efficacy and safety data in these populations.

Multimorbidity, polypharmacy, specific aspects related to aging complicate the transferability to real life of the data obtained on the average population, which is usually represented in traditional clinical studies, and may have involve significant deviations in the benefit/risk profiles for established treatments or make such profile uncertain for innovative medicines.

The topic relating to the elderly and ultra-elderly populations in the submitted projects shall cover at least one of the following lines of research, also integrating several lines of research in the same project and preferably through carrying out *ad hoc* clinical studies:

- Adjustments of posology and therapy schemes to reduce the burden in ultra-elderly patients, maintaining efficacy at adequate levels.
- Clinical studies aimed at evaluating interactions between medicinal products.
- Studies aimed at studying the impact of de-prescribing in multimorbid patients.
- Studies with cellular therapies in elderly populations.
- Clinical studies on depression, refractory/resistant depression in the elderly population.
- Dementias: cognitive studies of treatment and coexistence of cardiovascular and metabolic problems.
- Clinical studies on therapeutic strategies aimed at prevention of fragility and/or progression from fragility to disability, standardization of the therapeutic approach in elderly and ultra-elderly patients.
- Methodological models for the study of efficacy/risk of medicines in the case of multimorbidity and polypharmacy in elderly and ultra-elderly populations.

Thematic area 5 – Antimicrobial Resistance

The clinical studies submitted in this thematic area should focus on questions which can produce useful evidence in the clinical management of the problems related to antimicrobial resistance and which can have positive effects on the NHS at the same time, so reducing the emergence and spread of infections caused by pathogens resistant to antimicrobial medicines with consequent impact on the costs for their management.
The studies should be aimed at streamlining use of old and new medicines and at identifying therapeutic strategies with the final goal of prevention, reduction and containment of the onset of drug-resistant infections. Several published data available in literature concern hospitals, where such problem has a significant impact on mortality, morbidity and reduction of available treatment options. With reference to antibiotic-resistance, considering that the problem is not confined to hospital facilities alone and that the incorrect use of antibiotics and/or their abuse is also found in extra-hospital settings, in long-term care facilities and in general medicine, it is desirable that projects in this thematic area also involve non-hospital facilities. The topic in the submitted projects shall cover at least one of the following lines of research, also integrating several lines of research in the same project:

- Development, adoption and evaluation of the effectiveness of strategies for the appropriate use of antimicrobials (e.g. antimicrobial stewardship programs in hospitals).
- Studies aimed at implementing and evaluating strategies to optimize the use of antibiotic therapy in extra-hospital settings, such as general medicine and long-term hospitalization facilities.
- Head-to-head comparison and studies to evaluate the specific tissue concentration between antibiotics for the purpose of defining the place in therapy and the best cost-effectiveness of treatments.
- Identification of predictive response markers that can be used for the optimal use of antibiotics.
- Identification of diagnostic pathways that optimize the efficacy and cost-effectiveness of antibiotic use.
- Clinical studies on the interaction between antibiotic use and antifungal resistance.
- Appropriate use strategies of antifungals.
- Strategies for using antifungals within stewardship programs for antibiotic use.
- Strategies for reducing resistance to antivirals.

Subjects eligible for funding

The proposed studies shall comply with the requirements for non-profit studies pursuant to Decree of the Ministry of Health 17 December 2004 and shall have the character of clinical studies (and not preclinical or concerning mechanisms of action) on medicines of fundamental interest to the NHS. Funding for research projects is aimed at public and private non-profit organisations.

Please note that in order to participate in the AIFA call for proposals 2017, it is necessary to have an in-depth knowledge of the reference legislation governing clinical research in Italy, for the purpose of a correct application of the same during the authorization and carrying out of the study.

General information on the call for proposals

In this call for proposals converge the dedicated amounts deriving from the estimated budget for the year 2017 (budget 2017) and those from the final budget for the year 2016.

Applications for participation in the AIFA call for proposals 2017 must comply with the following criteria:

1. The call for proposals is open to public and private subjects that operate in the field of health care and scientific research and which are non-profit-making (which must be clearly stated in their founding act).
2. Each proposer may present, as Principal Investigator, only one study protocol.
3. The operating units will not be able to participate in more than 3 protocols in total.
4. Protocols will not be accepted whose proposer has had a project financed (as Principal Investigator) in the AIFA calls 2012 and 2016.
5. The projects funded may not last longer than 36 months, including the preparation of the Final Study Report, in order to ensure real effects on the NHS in good time.
6. In order to support the priority of clinical research, protocols will not be considered whose main objective is the study of the mechanisms of action of medicines. However, it is acceptable the presence in the clinical study of evaluations aimed at identifying specific markers in order to identify subgroups of responder populations and/or with high risk of adverse reactions, provided that the feasibility and the main purpose of the project are not changed.
7. The protocols will be excluded from the final list, the content of which is considered, at the sole discretion of the Board of Directors of AIFA, overlapping one of the projects already approved with the previous AIFA calls. The list of projects approved under the previous AIFA calls can be consulted on the AIFA website **www.agenziafarmaco.it**.
8. After communication of the evaluation results, the Principal Investigators of the selected studies shall commit to sign the contract and to submit all the documentation to AIFA and to the Ethics Committees within 60 days from receiving the communication letter from AIFA, in order that the study start as promptly as possible.
9. In the case of multicentric studies, the operating units participating in the study must declare the number of patients assisted in the center in the last two years for the clinical condition under study. Based on this data, the likely estimates of patient recruitment to be included in the study should be provided.
10. In the case of multinational studies, AIFA funding may be only for the Italian quota, provided that this is a study with the characteristics of independent research (for further information, see the paragraph "Participation of Italian research groups in international studies").

11. The study medicines in their off-label use cannot be charged to the NHS.
12. In order to guarantee continuity in the conduct of the study project throughout its duration, the person who has reached the retirement age limits and/or who is close to retirement in the three years planned for the study cannot act as the Principal Investigator coordinator.
13. Protocols shall be submitted exclusively by electronic means through the link **http://aifa.cbim.it**.

Similarly to the previous calls, the possibility of co-financing by companies or public and private entities with an interest in supporting the independent AIFA research program is possible also for the call for proposals 2017.

In particular, co-financing by private companies is allowed only as follows:

a) Medicines reimbursed by the NHS can be provided in case of a packaging modality for a "blind" administration.
b) Medicines for off-label uses may be provided.
c) Companies or public and private bodies may co-finance the individual thematic areas. The statement of availability to co-financing by the potential sponsor must be submitted within the deadline for submission of the protocols. This co-financing will be divided equally between all the selected protocols of the call for the thematic area covered by the co-financing.
d) Public bodies and non-profit organizations and/or associations may also co-finance individual studies; the statement of availability to co-financing must be submitted within the deadline for submission of the protocols

If the costs for supplying the medicines (points "a" and "b") are provided by a pharmaceutical company, the readiness of the company shall be submitted in writing. Such availability must be included in the documentation attached to the application form ("budget" section) together with submission of the study protocol.

At the time the protocols are presented, all the contributions obtained as co-financing must be declared.

Submission of applications

The protocols (in English) are to be submitted **by 31 January 2018 - 6.00 pm (CET)** exclusively by electronic means, by clicking the link **http://aifa.cbim.it** on the AIFA website. For the purposes of acceptance, the date of receipt by the website will be taken as evidence.

Protocols submitted in other ways than those described above or sent beyond the limit indicated above or incomplete with regard to the compilation of mandatory fields will not be admitted to the evaluation.

The Guidelines and the application form for drafting and presentation of the protocol can be found in Annex 1 to this call for proposals.

Participation of Italian research groups in international studies

The AIFA call for proposals 2017 also includes the possibility to submit, within the thematic areas of this call, funding requests for the participation of Italian research groups in international multicentric research projects having the necessary characteristics to be included in the typology of studies "independent research", according to the Italian non-profit law.

These proposals shall be submitted according to the general terms of the call. The submission of the protocol for the activities carried out by the Italian center(s), however, shall be accompanied by the complete protocol of the study and by any information on its registration in one of the recognized international clinical trial registries as well as by information on the authorization status of the protocol in other countries.

Transparency and independence of selection procedures

A single evaluation phase of the proposals is envisaged, to which will be admitted the protocols submitted by the specified deadline and for which AIFA will have verified compliance with the requirements set by the call 2017.

The funding shall be provided on the basis of a ranking of scientific merit of the projects assessed as sufficient until the available fund is exhausted, but in any case within a final evaluation score corresponding to the excellence of the project submitted.

In the selection phase the principle of transparency will be respected, making public both the criteria for the decisions and the results of the selection process.

Evaluation method

Only protocols complying with the requirements of the call for proposals shall be admitted to the evaluation procedure. Any cases of non-compliance with the requirements of the call for applications will cause exclusion from the competition.

In case of false declarations, the study project may be excluded from the ranking even after the conclusion of the evaluation. The applicant is responsible for any false declarations pursuant to art. 46 and following of the D.P.R. 28 December 28 200 No. 445 and for the consequent penal sanctions referred to in art. 76 of the same D.P.R.

The evaluation will be carried out by international auditors, using the research workflow of the Ministry of Health, which allows a blind coupling, according to specific thematic areas, between the protocols and the international auditors automatically selected by the workflow on the base of the expertise in the specific subject. Each protocol will be evaluated blind by two auditors, who will assign a score based on the criteria defined in the list in Annex 2 of this call ("Guidelines for the evaluation of independent research protocols").

Prior to the evaluation of each individual protocol, the auditor will have to fill in the Declaration of Conflicts of Interest. After verifying the absence of conflicts of interest, the auditor will be able to proceed with the evaluation of the pertinence of the study proposed to the topic of the Call for Proposals; if the study is found to be relevant, the auditor will proceed to formulate a score and a written evaluation on:

- Scientific relevance.
- Methodology/study design, reference bibliography.
- Level of innovation.
- Organization/experimental center.
- Principal Investigator (professional qualification).

For each criterion there is a score from 1 to 9, with 1 = exceptional and 9 = poor. The sum of the scores for the five aspects considered leads to the definition of the final score.

Based on these criteria, a score up to 5 corresponds to exceptionality, a score up to 10 corresponds to excellence, a score up to 15 corresponds to a very good/almost excellent level.

The scores of the two auditors will be compared blindly with a further verification electronic procedure, at the end of which a single score can be defined or two different scores, one per auditor. In case of differences between the two auditors for which an agreement cannot be reached by comparison, the study will maintain the double score and will be submitted to a third verification phase during the next Study Session phase. The adequacy of the budget and the impact on the NHS of all the studies submitted shall be evaluated during the Study Session. The final evaluation phase shall be carried out through a plenary discussion by the Study Session, composed of independent national and international experts, and will lead to the definition of the final score for each study and to the final list of the proposals based on the final score obtained.

The successful projects of the call for proposals shall be those with a score corresponding to the excellence of the project presented in order of ranking and until the available resources are exhausted. Should the entire amount of resources be not allocated, the residual quota will be automatically transferred to the resources for 2018 AIFA call for proposals for independent research.

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

- Principal Investigator not successful in previous AIFA calls.
- Principal Investigator related to an experimental center not successful in previous AIFA calls.
- Age of the Principal Investigator.