ANNEX 1

AIFA CALL FOR PROPOSALS 2018
FOR INDEPENDENT RESEARCH INTO MEDICINAL PRODUCTS

Guidelines for drafting the Protocol Form

AIFA CALL 2018

Introduction and general information
The study protocol must be written in English and contain all the details necessary for an accurate assessment.
Maximum accuracy is required in the drafting of the protocol also relating to the clinical study organization as this protocol will be attached to the Contract.
Specific details that may be relevant to better clarify the study protocol (e.g. reporting form, assessment scales, etc.) can be attached to the protocol. It is not necessary to include the documents submitted to specific evaluation by the Ethical Committees (e.g. informed consent).
In order to facilitate the work of the reviewers, a table with the list of all acronyms (e.g. Glasgow Coma Score, GCS) must be included.
Moreover, the study protocol shall be classified by the Principal Investigator as indicated in appendix A, in order that the study protocol is assigned to the reviewer with the most appropriate expertise by the research workflow.
All the sections should be filled in to allow a correct evaluation of both scientific and feasibility of the project.

Principal investigator (PI)
Please indicate the name of scientific manager and applicant for the Research Project for the AIFA Call, his/her birth date and fiscal code.

Funding in previous AIFA Calls
Please indicate if the PI has already obtained funding by AIFA in previous AIFA Calls and specify the year.

Study title
In addition to study title, the Running title (max *50* characters) should be noted.

Acronym title
An acronym title is possible (maximum *10* characters)l.

Keyword
Enter up to *5* keywords

Thematic area/Specific topic
Principal investigator must select only one thematic area and only one line of research (this latter when required). If a research project may have more than one thematic area/line of research the PI have to select the most representative ones.

Rare diseases
For projects within this area, PI has to indicate the list and the bibliographic rationale used to definite it.

Institutional Address
Please indicate the address of the Institution which applies.
Please attach a declaration that the applicant Institution is in compliance with AIFA Call requirements.
For successful projects, the Contract with AIFA will be signed by the legal representative of the Proposing Institution.

PI Centre Address (Public Institution or No Profit Institution)
Please indicate the address of the centre where Principal Investigator is permanently employed.
In case of multicentre studies the centre here indicated is the coordinating centre.

Operative Unit/Units Institutional Address
Please list all the Clinical Centres directly involved in patients recruitment and any Centres involved for other tasks/activities as statistics, management, etc. Please specify in detail name and address of the Collaborating Centres.
Please, pay close attention to indicate the correct name of Units.

Pharmacological Treatment
Please list every drugs used both in the treatment and in the control groups. If a therapeutic class is used instead of a specific drug, please indicate the class.
If a medicinal product is marketed in Italy or abroad, please specify if it will be used or not according to marketing authorization (Summary of Product Characteristics - SmPC), with particular reference to therapeutic indications; please indicate modification of packaging, formulation and other variations (except for re-labeling).
This section must also be filled in for observational studies on drugs and drug classes.
It should be reminded that the manufacturer of the investigational drug product must be GMP compliant.

Advanced therapy
Indicate if advanced therapies will be used or not. If yes, please specify if somatic cell-therapy medicines, gene-therapy medicines or tissue-engineered medicines will be used.

Study design and duration
Please choose the study design and indicate the number of patients to be recruited, enrollment time expected and study duration in months (from authorization by Competent Authority/Ethic Committee to last follow-up visit).

Synopsis (max 4,000 characters)
This section shall include: Background; Objectives; Methods; Expected results.

Background (max 4,000 characters)
Please describe an updated review of already available evidence in the relevant literature with reference to disease, available treatment and therapeutic regimen information on which the study is focused.

Rationale (max 4,000 characters)
Please describe the clinical question that will be the object of the study and what the study will add to the overall available evidence; the innovativeness of the study and the possible benefit/risk ratio.

Impact on the National Health Service (max 4.000 characters)
Please describe what the study will add to the overall available evidence, transferability to clinical practice, possible impact on the Italian National Health Service (NHS) and/or on study population.

THE FOLLOWING SECTIONS ARE RELATED TO STUDY PROTOCOL FOR INTERVENTISTIC/OBSERVATIONAL CLINICAL TRIAL

Objectives of the study (max 4,000 characters)

The purpose of the study, the primary and secondary objectives according to statistical hypothesis (superiority, equivalence or non-inferiority for the primary endpoint) shall be indicated.

Study design (max 4,000 characters)
Please describe the study design on the basis of the questions which are the object of the study proposal, phase of clinical trial (if applicable), study organization; if prospective/retrospective, controlled or not controlled; if superiority, equivalence or non-inferiority is expected.

Study population (max 4,000 characters)
The characteristics of the study population and the clinical context (hospital, general medicine, etc.) in which the study will be conducted, the procedure and the enrollment time shall be described. It should be specified whether special populations will be included in the study. Criteria and procedures for withdrawing from the study should be specified.

Inclusion criteria (max 4,000 characters) and Exclusion criteria (max 4,000 characters)
Please indicate in detail inclusion/exclusion criteria.

Intervention (max 4,000 characters)
It shall be provided detailed information on treatments (or other types of interventions) for each group (treatment and control) including:
• Dose (and dose increase) and dosage form, packaging and labeling of the investigational medicinal product;
• Duration of treatment (including number and duration of cycles, if applicable) and the follow-up period;
• Route of administration;
• Medicines/treatments allowed (including rescue medicines) and not allowed before and/or during the study;
• Procedures for monitoring compliance of the subjects;
• Description of the "stopping rules" or "discontinuation criteria" for each subject, for a part of the study and for the entire study;
• Experimental drug management procedures, including those for placebo and for the comparator drug, if any.

With reference to observational studies, please provide information on medicinal products/treatments under evaluation.

Endpoints and Outcomes (max 4,000 characters)
It shall be indicated primary and secondary endpoints and specific outcome measures; the procedure for the detection of the outcomes (with particular attention to the relationship between subjective and objective endpoint assessment and blindness); the rationale for supporting the validity of each surrogate or composite endpoints, if appropriate, and their clinical relevance.

Methods (max 6,000 characters)
A description of the measures taken to minimize/avoid bias, including (but not limited to):
Randomization. The methods used to generate the randomization sequence shall be indicated. Centralized randomization should be preferred; other randomization procedures should be adequately motivated. Include the procedures for the maintenance of randomization code list as well as the procedures for the code breaking and the identification of the therapies assigned to the subjects. A flowchart describing the comparison groups, allocation procedures, details on dose/duration of treatments and patient follow-up can be attached.
Blinding (masking). The presence of blinding and its modalities should be described. In particular, specify if blinding involves personnel for treatment administration and/or outcome assessors.
Data collection. It should be indicated the data that will be collected; the tools used for data collection and their validity and reliability; the measures/indicators used; the potential sources of distortion in the retrieval of information regarding study subjects interventions/treatments; the duration and frequency of follow-up; missing data management. When electronic Case Report Form (e-CRF) is used, only validated systems are acceptable that guarantee traceability (e.g. excel spreadsheets do not represent an adequate data recording system). Please include in this section the identification of source data.

Statistical Plan (max 4,000 characters)
Statistical hypothesis (superiority, equivalence or non-inferiority for the primary endpoint) shall be detailed.

Calculation of the sample size. Please indicate the estimate of sample size and how it is defined. The information required to calculate the sample size include potency, level of significance, incidence in the population under investigation and treatment effect size. The adjustment for other factors that affect the calculation of sample size (e.g. expected compliance rates) should also be reported. For equivalence/non-inferiority studies, the largest acceptable difference should be specified.
Statistical Analysis. Please describe the main statistical analyses that will be carried out. The definition of the populations for the main analysis and the probability of error should be indicated. A brief description of statistical techniques, additional methods of analysis, and possible analyses by subgroups should be provided. The main statistical analyses that will be used in the presentation of final results (e.g. final reports, publications) shall be consistent with this section. The planning of each interim analysis (if any) and the predefined study interruption rules shall be clearly indicated.
Please indicate the estimation of drop out patients and possible impact on study results.

Timing (max 4,000 characters)
Timing. Please indicate: the duration of the study (patients enrollment, duration of treatment, follow-up, etc.); timing of the possible interim analysis for the evaluation of the study.

Feasibility (max 4,000 characters)
Organizational characteristics. The participating centers, the specialties and the expertise necessary for carrying out the study should be described. In the case of multicenter studies, please specify:
•the institutions/unit responsible for study coordination, treatment assignment, and monitoring of the procedures;
•the presence of steering committees and/or monitoring committees for data and/or safety monitoring (if applicable);
•the presence and organization of centralized laboratories (if applicable).
Feasibility. Please indicate previous experience of the principal investigator, the operative units and the institution coordinating the study; relevant technology, instrumentation and characteristics of the experimental centre for the adequate conduction of the study.

Good clinical practices and Ethical aspects (max 4,000 characters)
Good clinical practice. Experimental studies shall be conducted in accordance with Good Clinical Practice (GCP). The specific risks of the study (e.g. risks for patients, complexity of study design, validity of collected data, etc.), risk minimization procedures (e.g. training activities, verification of eligibility before randomization, data verification, drug accountability, etc.), the characteristics and frequency of monitoring activities and the institution responsible for this task shall be discussed.
Ethical aspects. It shall be described the potential risks for study subjects with reference to physical/psychological aspects or to a possible excessive interference with the subject's privacy as well as the procedures to follow to prevent such potential risks. The documentation requested by the ethics committees should not to be attached.
Insurance. Please enter information on enforcement of the law on the study insurance contract (Ministerial Decree 14 July 2009).

References (max 4,000 characters max 20/25 references)
Only the references that are strictly relevant to the study proposal should be indicated. References should include authors (in case of more than 6 authors, report the first 3 authors followed by *et al.*), Title, book or journal, year, volume number and page numbers. For texts, also the publisher shall be indicated.

Budget
The budget must be consistent with the complexity of the study, and should be adequately motivated and detailed. Personnel related expenditures shall refer to the total number of person-months and be specified in detail for reporting purposes. For this reason, the time-person dedicated to the development of the project cannot overlap with other activities of the clinical center and must be counted as an exclusive activity. The cost for the medicinal products included in the trial shall not be reported in the budget, in case this cost is covered by the NHS. For the preparation of the budget, please refer to the attached guidelines (Appendix B). In addition to the description in the blank field, it is also required to fill in the table of costs included in the provided forms.

Institution agreement (max 2,000 characters)
The Principal Investigator must declare his/her availability to submit through the National Monitoring Centre on Clinical Trials all the documentation required by the applicable legislation. The documentation must be submitted to AIFA, as Competent Authority, and to the Ethics Committees within 60 days from

signature of the contract. Moreover, the Principal Investigator shall indicate the acceptance by his institution to participate in the study along with the agreement by the institution for the use of the human and technological resources described in the study protocol. The declaration of the Principal Investigator must be submitted with the study protocol**.**

Institution agreement with collaborating centres (max 4,000 characters)
The Principal Investigator must state the agreement with all involved centres in study protocol.

List of the investigators responsible for the units dedicated to data analysis and GCP monitoring of the study (max 4,000 characters)
Please report the researchers responsible for the units dedicated to data analysis and GCP monitoring of the study.

Submission of study protocol to Competent Authority and/or Ethic Committee
Please declare that protocol study not has already been submitted to the Competent Authority (CA) and/or the Ethics Committee (EC) for approval.

THE FOLLOWING SECTIONS ARE RELATED TO STUDY PROTOCOL FOR META-ANALYSIS

Objectives of the study (max 4.000 characters)
Please describe the primary objectives and the secondary objectives of the study. Provide an explicit statement of the question(s) the review will address with reference to outcomes, participant, interventions, study design and comparators.

Methods

- **a (max 4.000 characters)**
  Eligibility criteria: specify the study characteristics of population and criteria for eligibility for the review.
- **b (max 4.000 characters)**
  Information sources: describe all intended information sources: used electronic databases (electronic, contact with study authors, trial registers) and interval time considered.
- **c (max 4.000 characters).**
  Search strategy and methods for selecting studies: present draft of search strategy to be used and filter used. Describe the mechanism(s) at will be used to manage records and data throughout the review.

Study records (max 6.000 characters)
Data collection process and data items: describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators.
List and define all variables for which data will be sought.

Data- a (max 6.000 characters)
Synthesis: indicate criteria under which study data will be synthesized (e.g. risk ratio, mean difference, incidence rate). Describe methods of combining data from studies, including any planned exploration of consistency (e.g., I2, Kendall's tau). Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression).

Data- b (max 4.000 characters)
Describe methods used for assessing risk of bias of individual studies and how this information will be used in any data synthesis. Describe how the strength of the body of evidence will be assessed (e.g., GRADE).

References (max 4.000 characters or max 20/25 references)
Please report only the references that are strictly relevant to the study proposal. References should include authors (when there are more than 6 authors, report the first 3 authors only title, book or journal, year, volume number and page numbers. For books, the publisher should also be reported.

Budget
The budget must be consistent with the complexity of the study, and should be adequately motivated and detailed. Personnel related expenditures shall refer to the total number of person-months and be specified in detail for reporting purposes. For this reason, the time-person dedicated to the development of the project cannot overlap with other activities of the clinical center and must be counted as an exclusive activity. For the preparation of the budget, please refer to the attached guidelines (Appendix B). In addition to the description in the blank field, it is also required to fill in the table of costs included in the provided forms.

Institution agreement (max 2,000 characters)
The Principal Investigator must declare his/her availability to submit all the require documentation to AIFA and to the Ethics Committees, if applicable, within 60 days from signature of the contract. Moreover, the Principal Investigator shall indicate the acceptance by his institution to participate in the study along with the agreement by the institution for the use of the human and technological resources described in the study protocol. The declaration of the Principal Investigator must be submitted with the study protocol**.**

Institution agreement with collaborating centres (max 4,000 characters)
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List of the investigators responsible for the units dedicated to data analysis and GCP monitoring of the study (max 4,000 characters)
Please report the researchers responsible for the units dedicated to data analysis and GCP monitoring of the study.

DOCUMENTS TO BE ATTACHED

Declaration of conflict of interest (max 4,000 characters)
It shall be indicated whether the principal investigator was an employee, consultant, principal researcher, board member, advisory board member or member of an equivalent body for a company in relation to the concerned medicinal product (or to a medicinal product of the same therapeutic category) in the previous 3 years. All other financial ties with a company whose medicinal product is being studied (including stock options, fees, loans, etc.) have to be declared.
Please note that the filling in of the **Declaration of conflict of interest** is mandatory.

Curriculum vitae of the principal investigator
Description of the current position, the main work experiences and expertise in the research sector, with particular reference to the thematic area covered by the study proposal.
Bibliography
Please include the publications considered relevant, **with the respective impact factor**, for the Principal Investigator. Please note that the submission of **Curriculum vitae of PI** is mandatory.

Curriculum vitae of the investigators responsible for the units involved in the study
Description of the main work and experience in the research field. The complete list of clinical centres that can enroll patients can be attached to the study protocol.
Bibliography
Please include the publications considered relevant, with the respective impact factor, for each investigator of the units involved in the study.
Please note that the submission of **Curriculum vitae of the investigators responsible for the units involved in the study** is mandatory, if applicable.

Declaration on Compliance of Applicant Institution with AIFA Call requirements
The PI has to provide a Declaration on Compliance of Applicant Institution with AIFA Call requirements.
Please note that the submission of this declaration is mandatory.

Institution agreement
The Principal investigator must provide a declaration with the institution acceptance to conduct the study and agreement for the use of the human and technological resources described in the study protocol.

Please note that this declaration is mandatory.

Additional annexes

Additional annexes can be attached. Please include only details relevant for the evaluation of the study protocol. All appendices must be mentioned in the text of the study protocol and included in the same annex.