ATTACHMENT 1

AIFA CALL FOR PROPOSALS 2017
FOR INDEPENDENT RESEARCH INTO MEDICINAL PRODUCTS

Guidelines for drafting the study protocol

AIFA CALL 2017

Introduction and general information

The study protocol shall 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 auditors, a table must be inserted with the list of all acronyms (e.g. Glasgow Coma Score, GCS).

Moreover, the study protocol shall be classified by the Principal Investigator as indicated in appendix A, in order that the study protocol is assigned automatically by the research workflow to the auditor with the appropriate expertise.

Study title

In addition to study title, the Running title (max 50 characters) should be noted. In this section should be noted the protocol version and the date.

Title acronym

A title acronym is possible (maximum *10* characters)

Keyword

Enter up to *10* keywords

Sinopsys (max 4,000 characters)

This section shall include: Background; Objectives; Methods; Expected results.

Background -a (max 4,000 characters)

Description of the clinical condition on which the study is focused and of the evidence supporting the rationale.

Background -b (max 4,000 characters)

Information on the medicine/medicines/therapeutic treatment which are the subject of the study proposal.

Rationale -a (max 4,000 characters)

Indicate the clinical question which is the objective of the study and what the study shall add to the available evidence.

It should be paid particular attention to describing the possible impact on the National Health Service (NHS) and/or on the studied population, the innovativeness of the study proposal and the possible benefit-risk ratio.

Objectives of the study (max 4,000 characters)

The purpose of the study, the primary objectives and possibly the secondary objectives of the study, and the statistical hypothesis (superiority, equivalence or non-inferiority for the primary endpoint) shall be indicated.
(*The following sections shall allow assessment of the scientific validity and feasibility of the study*).

Study design (max 4,000 characters)

Describe the methodology applied on the basis of the questions which are the object of the study proposal and of the performance of the study.

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 fragile populations will be included in the study. Criteria and procedures for withdrawing from the study should be specified.

Inclusion criteria (max 4,000 characters)

Exclusion criteria (max 4,000 characters)

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 pharmaceutical 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.

Outcomes (max 4,000 characters)

It shall be indicated: the primary and secondary 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 endpoint, if appropriate (a brief comment on the clinical relevance of the endpoints mentioned above should be included).

Methods-a (max 4,000 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 (including the modalities for the maintenance of the randomization codes envisaged for the study as well as the procedures for the opening of these lists and the identification of the therapies assigned to the subjects).

Blinding (masking). The presence of blinding and its modalities should be described.

A flowchart describing the comparison groups, allocation procedures, details on dose/duration of treatments and patient follow-up can be attached.

Methods-b (max 4,000 characters)

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 the subjects of study and the interventions/treatments; the duration and frequency of follow-up; the estimated amount of subjects lost to follow-up and the possible implications for the results of the study. In cases where the use of an electronic clinical signaling module (e-CRF) is envisaged, 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 the definition of the source data.

Methods-c (max 4,000 characters)

Calculation of the sample size. Please indicate the estimate of the sample size and the way it is determined. The information required to calculate the sample size includes the potency, the level of significance, the incidence in the population under investigation and the size of the treatment effect. Also the adjustment for other factors that affect the calculation of the sample size (e.g. expected compliance rates) should also be reported. For equivalence/non-inferiority studies, the maximum permissible difference should be specified.

Statistical Analysis. Please describe the main statistical analyzes 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 analysis by subgroups should be provided. The main statistical analyzes that will be used in the presentation of the final results (e.g. final reports, publications) shall be consistent with the content of this section. The planning of each interim analysis (if any) and the predefined study interruption rules shall be clearly indicated.

Methods-d (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 multicentric studies, please specify:

• the institutions/unit responsible for the coordination of the study, the assigned treatment, the monitoring of the procedures;

• the presence of steering committees and/or monitoring committees for data and/or security monitoring (if applicable);

• the presence and organization of centralized laboratories (if applicable)

Feasibility. Please indicate: previous experience of the main researcher; previous experiences of the institution coordinating the study; technology, instrumentation and characteristics of the experimental center relevant for the proper conduct of the study.

Methods-e (max 4,000 characters)

Timing. Please indicate: the duration of the study (enrollment of patients, duration of treatment, follow-up, etc.); timing of the possible interim analysis for the evaluation of the study; expected time of submission of the final report. In this section, enter the estimate of the total duration of the study starting from the first visit date of the first patient.

Good clinical practices. 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 the study design, etc.), risk minimization procedures (e.g. training activities, verification of eligibility before randomisation, data verification, accounting of the medicine, 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 to the study subjects related to the physical/psychological aspect 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 need not to be attached.

Insurance. Please enter information on enforcement of the law on the study insurance contract (Ministerial Decree 14 March 2009).

Bibliography (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 magazine, year, volume number and page numbers. For texts, also the publisher shall be indicated.

Budget (max 4,000 characters)

The budget must be consistent with the complexity of the study, adequately motivated and detailed. Staff costs shall refer to the total number of person-months and be specified in detail for reporting purposes. To that end, the time-person dedicated to the development of the project cannot overlap with other activities of the experimental center and must be counted as an exclusive activity. The cost for the medicinal products included in the trial shall not be incorporated into the budget, in case this cost is covered by the NHS. For the preparation of the budget, please refer to the guidelines attached with 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 forms provided.

Institution agreement (max 4,000 characters)

The Principal Investigator shall declare his/her availability to submit through the Clinical Trial Observatory all the documentation required by the applicable legislation. Such declaration shall 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 shall be submitted with the study protocol; the institution agreement shall be made available by the date of signature of the contract**.**

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 scientific supervisor of the study.

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 centers 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 researcher of the units involved in the study.

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 - Make sure to comply with the requirements.

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 product concerned (or to a product of the same therapeutic category) in the previous 3 years. All other financial ties with a company whose 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.

Attachments (only if relevant)

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.

Additional forms

In case of insufficient availability of characters for the individual forms relating to the study protocol, additional information can be uploaded in the appropriate section of the information system. This shall be adequately identified by the applicant on the basis of the additional content.