



2019 Call for Proposals

Single cell approaches for the study of oncogenic processes

The Cancer ITMO of the French National Alliance for Life and Health Sciences (AVIESAN), in collaboration with the Institut National du Cancer (French National Cancer Institute) and Inserm, implements the research section of the cancer plan.

Online submission: <https://sp2013.inserm.fr/sites/eva/appels-a-projets/Pages/default.aspx>

Deadline: 30th April 2019

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1 CONTEXT AND OBJECTIVES OF THE CALL FOR PROPOSALS

Remarkable technological advances of recent years have changed our global understanding of Cancer through scientific and therapeutic point of view. The heterogeneity of the tumour cells results in a clonal evolution, especially that of genetic and epigenetic evolution, which is modulated during the progression of the disease, by the treatments received and the metastatic dispersion. The extracellular matrix, the stromal and immune cells as well as the secreted cytokines and chemokines form a microenvironment more or less favorable to the emergence of a malignant clone and its spontaneous evolution, or under treatment. The development of new technologies to harness genetic, epigenetic, transcriptomic and proteomic information at the cellular level, known nowadays under the term "single cell approach", makes it possible to better understand the heterogeneity of tumors. This helps in the understanding of factors that regulate tumor progression, their response to treatment, the occurrence of metastases and recurrences. The challenge lies not only in the isolation of cells but also in the development of sufficiently sensitive analytical methods to detect poorly represented signals, which require elaborate mathematical procedures. In addition, the natural microenvironment and its complexity must be considered.

This funding call is organized by ITMO Cancer of the French National Alliance for Health and Life Sciences (Aviesan) and the operational management is entrusted to INSERM.



This call for proposals aims to promote research in oncogenesis based on "Single Cell" approaches to identify or characterize factors that promote the emergence and progression of tumours, be it tumor clone population or microenvironmental cells. Whenever possible, the projects should aim at promoting the transfer of the results to clinical applications and evaluate the contribution of these approaches to therapeutic treatment in oncology.

All projects (including its description, objectives, budget and strategy) applied in conformity to the current funding call can obtain a single funding from Plan Cancer irrespective of the financing operator (Inserm for ITMO Cancer AVIESAN, INCa or DGOS). In case, the same project is selected for funding by different funding calls of Plan Cancer, then the co-ordinator assures that he selects one funding call and desists the others. Otherwise, only the project with a higher budget will be retained and all other funding (s) obtained under the Cancer Plan must be fully reimbursed. Similarity is established, when the project in question has identical main objectives and approaches, and involve teams that are mainly identical.

2 SCOPE OF THE CALL FOR PROPOSALS

The concerned investigators are biologists, mathematicians, bioinformaticians, physicists, biochemists and clinicians working in basic or applied research. The project should describe precisely the conditions of analysis and storage of the data generated.

The following research topics fields are eligible:

-  **Single cells analysis** from fresh human tumours, or after xenografting, culture of organoids, culture of stem cells reprogrammed from human tumours, or from animal models,
-  **Single cell analysis** studying intra-clonal competition, either spontaneous or under the effect of a treatment,

- ✚ **Single cell analysis** in tumour microenvironmental studies,
- ✚ Mathematical or bioinformatic analysis of the data obtained from **single cells**,
- ✚ Integration of data obtained on **single cells** through global approaches (data mining).

The following projects are out of scope:

- ✚ Projects limited to improving an existing single cell isolation technique,
- ✚ Single cell approach projects reduced to microscopy and/or cell labelling,
- ✚ Clinical trial projects.

3 CRITERIA FOR ELIGIBILITY AND PROJECT EVALUATION

For each project submitted, the participating teams shall designate a scientific coordinator for the project. **The scientific Coordinator is a physicist, biologist or a mathematician working on projects contributing towards a better understanding of cancer.** In addition to his or her scientific and technical role, the coordinator is responsible for setting up the procedures for the collaboration between the participating teams, for the production of the required documents (reports and assessments), holding meetings, the progress and the communication of results. Applications from early-stage scientific coordinator are strongly encouraged.

For each project submitted, the participating teams shall designate their management body to receive the funding (which can be different from the body that the coordinator belongs to). The management body is contractually liable to Inserm for implementing the contract, forwarding all of the financial and scientific reports provided for in the agreement.

3.1 Criteria for eligibility

In order to be eligible, the projects must satisfy the following conditions:

- ✚ The project must meet the objectives of this call for proposals and fall within one of the themes identified in section 2,
- ✚ The project must have a duration of **24 to 36 months**,
- ✚ The project may be undertaken by a **single team or a consortium consisting of maximum 3 teams** that belong to different research disciplines, units and/or bodies,
- ✚ The project Coordinator must be a permanent researcher of a public body or of a higher public education institute. He/she must spend **at least 30%** of his/her time on the project,
- ✚ The Coordinator's managing body should be a public-sector research institution, an institution of higher learning or a public health institution or a recognized public utility research foundation. The managing body of the project Coordinator must not be an association. For precision, you can refer to section 5.3,
- ✚ The application file must be duly completed and include the required documents, and comply with the submission procedures mentioned in section 6.

3.2 Criteria for evaluation

After the eligibility criteria have been verified, the applications are submitted for a written evaluation by international experts and at least one reviewer from the assessment committee, the members of which

do not have any conflict of interests and do not present a project. Projects which do not meet the eligibility criteria will not be assessed. After publication of the list of projects selected, the membership of the assessment committee will be posted on the EVA website of Inserm. The opinions of the committee and experts will be sent at the request of the project co-ordinator.

The criteria for evaluation are:

 **Innovation and development:**

- Innovative nature (strategy, concept, technology, etc.),
- Perspectives in terms of later developments.

 **Scientific qualities:**

- Project relevance and originality,
- Positioning of the project in the national and international context,
- Clarity of the objectives.

 **Coordinator and participating teams:**

- Skills of the coordinator in his/her discipline
- Complementarity and/or multi-disciplinarity of the various teams associated with the project,
- Organisation of collaboration between candidate groups, planning review document production, holding follow up meetings and formatting results.

 **Methodology and feasibility:**

- Methodological relevance,
- Project environment (human resources, host structure),
- Credibility of the project's calendar and of the financing requested.

4 CALENDAR OF THE CALL FOR PROPOSALS

Date of publication of the call for proposals	February 2019
Opening of project submission site	March 14th, 2019
Deadline for submitting application files	April 30th, 2019
Tentative meeting date for the evaluation committee	September 2019
Tentative date for publishing the results¹	September 2019
Maximum start date of the project	December 2nd, 2019

¹ Results will be published on the EVA website : <https://sp2013.inserm.fr/sites/eva/appels-a-projets/Pages/default.aspx>

5 ADMINISTRATIVE AND FINANCIAL RULES

Preliminary article - Definitions:

Granting Act: Funding agreement or letter by which Inserm notifies the Managing Body of its rights and obligations with respect to conduct of the selected Project. The Granting Act takes the form of a notification letter if the body managing the grant is Inserm. These two instruments are hereafter referred to with the generic term "Granting Act".

Research Charity: a private body subject to the Law of 1901 devoting at least 50% of its main activity to research.

Managing Body: Research body managing the grant to conduct the Research Project as submitted in the Application File. The Managing Body is contractually responsible for implementing the Contract and compiling all the scientific and financial reports stipulated in the Granting Act.

Project Coordinator: the person responsible for the scientific conduct of the Project as designated in the Granting Act.

Research body: This term refers to all entities such as public sector research institutions (EPST, EPIC, etc.), institutions of higher learning (universities, etc.), research foundations, health care establishments, and any other body involved in the research field.

Partner: A research team contributing to conduct of the Research Project.

Project: research project addressed in the scientist's Application File and selected by Inserm for funding in the framework of the Cancer Plan.

Rules: these financial rules with their appendices.



5.1 Scope

These Rules apply to Managing Bodies allocated a grant by Inserm to conduct a Research Project, selected in a tender for projects launched by Inserm. Tender procedures are conducted by Inserm under the aegis of the following divisions: ITMO Cancer and the *Département de l'Évaluation et du Suivi des Programmes* (DESP, Department of Programme Evaluation and Monitoring) within the framework of the Cancer Plan 2014-2019.

5.2 Contents

Funding is granted by Inserm after the Project has been selected on the basis of the Application File submitted by the Coordinator according to the criteria for eligibility and evaluation of the text of the corresponding tender for projects.

The Application File includes:

-  A scientific file,
-  The Project's budget broken down in the financial appendices. The financial annexe should be uploaded as an Excel document **AND** as a **signed and stamped PDF** version. **The total budget requested should be coherent between the online Financial form, the financial annexe and the scientific file,**

- ✚ The CVs of the Project Coordinator and the Director(s) of any associated team(s) (all in a single file) **which respect the template provided on the EVA3 website**,
- ✚ The Administrative Form to be filled in online on the special Application File Submission site:
 - The online Administrative Form must be filled in for each participating team **whether funding is requested or not**
 - The online Financial Form must be filled in for each team requesting funding
- ✚ The bank statement of each Managing body.

For research charities, the following complementary documents should be appended to the Application File:

- ✚ Previous year's accounts together with forecasts and a financial plan, all following Inserm models.



All incomplete projects will be considered administratively ineligible.

5.3 Managing Bodies

Teams belong to the following bodies:

- ✚ Public-sector research institutions (EPST, EPIC, etc.),
- ✚ Institutions of higher learning (universities, etc.),
- ✚ Research foundations,
- ✚ Public-sector health care establishments,
- ✚ Other bodies involved in the research field.

Public research teams affiliated with a **public-sector body or entity** must have their grant managed by their associated public body or one of the mixed administrators of their structure.

The participation of **industrial partners and/or foreign teams** is possible as long as they provide their own funding in the Project.

The funding of charities (as defined in the 1901 Law) not classified as **Research Charities** is not allowed. Management via a charity is only possible if it justifies research activity.

Similarly, Inserm will check the capacity of charities to finance the part of the cost, which is self-financed. In the course of the selection process, Inserm may check that any partner charities in the Research Project are in a position to finance the part of the cost of the research not covered by the Inserm grant.

When administrative and financial files are being finalised, charities allocated a grant may be asked for further information.

If the Project involves different teams associated with different bodies benefiting from part of the funds granted, each Managing Body will sign a separate agreement with Inserm.

5.4 Coordinator

If there are multiple teams involved², a Project Coordinator must be appointed. Each partner team appoints a scientific leader.

² Refer to eligibility criteria

In addition to his/her scientific and technical role, the Coordinator is responsible for organising the collaboration between participating teams and meetings as well as monitoring progress and communicating results. He/she is responsible for compiling the required reports and sending them to Inserm. The Coordinator must:

- ✚ Be a statutory employee of a public-sector research body, a public institution of higher learning or a public health care institution and
- ✚ Devote at least 30% of his/her time to the Project.

5.5 Duration of the Project

The Managing Body and the Coordinator undertake that the Project will be completed within the time frame stipulated in the Granting Act notwithstanding possible modifications in duration detailed in Article 6.

This duration corresponds to that in which expenses must be assumed and paid.



The Project must begin before 2nd December 2019.

5.6 Granting Act

5.6.1 **Form of the Act**

The Act takes the form of:

- ✚ Either a grant agreement signed by the Managing Body and Inserm,
- ✚ Or a notification letter sent to the beneficiaries if the Managing Body is Inserm.

5.6.2 **Obligatory Information that must be mentioned in the Granting Act**

The Granting Act is compiled by Inserm on the basis of **information in the Application File and the text of the corresponding Tender for Projects.**

It must include the following information:

- ✚ Title of the Project,
- ✚ Duration of the Project,
- ✚ Duration of the Granting Act,
- ✚ Partners involved in the Project and the Coordinator,
- ✚ The total sum granted and how it is to be paid,
- ✚ The obligation to send Inserm the reports mentioned in Article **5h** of the Rules. How and when these are to be sent are stipulated in the Granting Act,
- ✚ Appendices to the Granting Act:
 - Appendix 1: summary of the Project as stipulated in the Application File,
 - Appendix 2: budget,
 - Appendix 3: model of the financial justification.

5.6.3 Documents constituting the Granting Act

The documents that make up the Granting Act have the following order of precedence, especially in the event of conflicting provisions:

- ✚ The Granting Act and its appendices,
- ✚ The Rules.

5.6.4 Special provisions

Inserm and the Managing Body may include in the Granting Act special obligations and/or exemptions from the Rules that are justified either by specificities of the funded Project or by modification of the Project in the framework of the Tender for Projects or by an agreement between Inserm and one or more of its partners.

5.6.5 Notification of the Granting Act

The Granting Act is notified by a letter from Inserm.

5.6.6 Modification of the Granting Act

Inserm will compile and sign an additional clause for any modification of the provisions of the Granting Act. However, prolongation of the duration of the Project, agreed to on an exceptional basis, is notified by a simple letter sent to the grant's Coordinator or Managing Body. The request for extension must be sent in writing by the Coordinator **within 6 months** of the end of the Granting Act.

Prolongation cannot exceed **12 months**.

5.7 [Grant](#)

5.7.1 Calculation of the total sum

When the total sum granted is identical to that asked for in the Application File, it includes the budgetary appendix compiled by the Coordinator when the application is submitted.

If the total sum granted by Inserm differs from that asked for in the Application File, Inserm sends the Coordinator an E-mail with the global total of the grant that it is intending to attribute to conduct the Project. In this case, a new financial appendix is compiled, dated and signed by the Managing Body. Then the Coordinator must conduct the Research Project in line with the instructions of Inserm.

In the event of refusal to compile a new financial appendix or failure to answer within one month of Inserm sending the E-mail, no grant will be attributed.

The grant attributed cannot be less than 25,000 € per team participating in the Project for its entire duration.

5.7.2 Value Added Tax

Because of the absence of counterpart to Inserm's financial support and applying the provisions of fiscal instruction 3A-4-08 of 13 June 2008 from the Public Finances Directorate, the grant attributed by Inserm is not subject to VAT.

5.7.3 Payment

5.7.3.1 Schedule

For Managing Bodies other than Inserm, 80% of the grant is paid on signing of the agreement with the remaining 20% paid after validation of the reports referred to in Article **5h**.

For charities, a first payment will be made on signing of the Agreement. Subsequent payments—up to 80% of the grant—will be made after the validation of interim reports (scientific and financial). Payment of the balance of 20% will be made after validation of the final reports.

When the Managing Body is Inserm, credits corresponding to the grant are opened in annual blocks.

5.7.3.2 Suspension of payment

If the project has not been started by the planned date of production of the first scientific report, Inserm will notify the Managing Body of the breach in a registered letter with acknowledgement of reception. This letter will require the Managing Body to overcome the difficulties encountered within two months of reception of this letter. If the deficient Managing Body has failed to remedy the problem by this deadline, cancellation is announced.

5.7.4 Use of the grant

The Managing Body must use the grant paid by Inserm exclusively to conduct the Project stipulated in the granting agreement.

At the end of the Project, any unspent moneys are to be reimbursed to Inserm within 90 days.

5.7.5 Eligible expenditure

All expenditure must be directly related to the Project, strictly necessary to its conduct and duly justified.

5.7.5.1 Equipment

Equipment other than the office materials and structures are authorised.

Apart from funds allocated within the framework of *Actions Equipement des Nouveaux Centres* (New Centre Equipment Actions), Inserm does not fund equipment costing more than a total of 50,000 € (not including tax). For expenditure of a greater amount, co-funding will have to be sought.

5.7.5.2 Staff

Expenses for temporary staff are eligible.

For private-sector establishments, expenses for permanent staff members are eligible as long as these employees are allocated to the Project strictly within the framework of its execution.

Funding **doctoral contracts is not allowed** unless this is specifically allowed for in the text of the tender for the project concerned.

Expenses for administrative staff are ineligible.

5.7.5.3 Operating costs

a. Services





The Coordinator may sub-contract out part of the Inserm-funded work required for the Project to third-party service providers. However, these services must only bear on execution of a small part of the Project and must comply with public-sector ordering regulations.

b. Consortium agreement

The cost of compiling a consortium agreement is eligible if the conditions stipulated in Article **5m** of these rules are fulfilled.

c. Other operating costs

The other operating costs that are eligible are:

-  Consumables,
-  Project-related travelling expenses for scientists,
-  Intellectual property expenses for patents and licenses resulting from execution of the Project,
-  Expenses justified by an in-house billing procedure.

5.7.5.4 Management costs

A fraction of general administrative costs generated by the Project may appear in the funded expenses.

This fraction is limited to 8% of the Project's grant total cost of eligible expenses and does not need financial justification.

5.7.5.5 VAT

For partners who are not subject to VAT or only partly subject, the unrecoverable part of VAT paid out on eligible expenses constitutes an eligible expense.

5.7.6 **Fungibility**

The grant paid by Inserm is fungible under the operating expenses ticket. Budget can only be transferred for staff costs with the agreement of Inserm.

5.7.7 **Other provisions**

If the amount of the grant paid by Inserm does not cover all expenses incurred in executing the Project, the Managing Body undertakes to complement the funding to ensure the Project's proper execution, either from its own resources or by means of one or more co-financing agreements.

In this event, the Managing Body will tell Inserm about any co-financing agreed to subsequent to notification of the agreement together with the name of the co-financer and the sum of the co-financing. In case the funding is from other funding call of Cancer Plan, Inserm will study this request and may revise the amount initially allocated accordingly.

5.8 Scientific and financial reports

5.8.1 **Scientific reports**

The Coordinator is to issue reports as stipulated in the Granting Act.

They are to be sent:

- ✚ An Interim Report six months after the beginning of the Project for Projects conducted by ITMO Cancer and DESP;
- ✚ A Mid-Term Report half way through the Project for Projects lasting more than two years;
- ✚ A Final Report within two months of completion of the Project.

Failure to produce interim or final scientific reports will entail reimbursement of all sums paid by Inserm.

Scientific review of interim or final reports may lead Inserm to ask for complementary information and financial support may be suspended or terminated in the event of failure to adhere to the Project or use of the funds for some other project.

5.8.2 Financial reports

Financial reports are compiled as stipulated in the Granting Act and the Rules; these present the expenses allowed throughout the duration of the Project.

Charities send an interim financial report on the anniversary date of the Granting Act.

Managing Bodies will issue a Final financial Report within two months of completion of the Project.

Financial reports are signed by the Coordinator together with a financial manager in such a way as to represent the Managing Body.

They are to be sent to Inserm by the grant's Managing Body.

Costs related to the certification of expenditure by an external auditor are eligible expenses.

At the end of the Project, any sums remaining will be paid back to Inserm by the Managing Body.

5.9 Other undertakings on the part of the Coordinator and the Managing Body

The Coordinator is obliged to tell Inserm about any substantial change to the Research Project vis-a-vis the contents of the Application File/Granting Act as well as about any difficulties encountered with conduct of the Project.

The Coordinator also undertakes to take an active part in operations to monitor the Project organised by Inserm/ITMO Cancer (dissemination workshops, colloquia, etc.).

The Managing Body will inform Inserm of any change of address or bank details.

5.10 Organiser - assigned accountant

The organiser of grants and credit transfers is Inserm's Président Directeur Général or by proxy its Director of Finance.

The assigned accountant for payments is Inserm's Head Accountant (*Agent Comptable Principal*).

5.11 Technical and financial supervision

At any point during the Project, Inserm reserves the right to organise site visits in concert with the Managing Body and the Project Coordinator.

Use of the grant paid under the aegis of the Granting Act may, throughout the Project and for two years after its termination, be controlled or audited by Inserm or by an agent appointed by Inserm, by means of a document review or an on-site inspection.

The Managing Body will be expected to be able to justify allocation of funded staff members to the Project as well as all expenditure on the grant.

The Managing Body must be ready to provide all administrative, accounting and legal documents as well as receipts related to use of the grant.

Attention is drawn to the fact that, since this grant corresponds to public moneys, the funds may be audited by various state supervisory bodies.

5.12 Publications – communication

5.12.1 Publications

All publications resulting from the Research Project must mention this financial support in the following terms:

"With financial support from ITMO Cancer AVIESAN (*Alliance Nationale pour les Sciences de la Vie et de la Santé*, National Alliance for Life Sciences & Health) within the framework of the Cancer Plan"

Any publications are to be sent to Inserm in a timely fashion (within five days of publication).

5.12.2 Dissemination of the abstract

The Coordinator will authorise the dissemination of the abstracts (in both English and French) contained in the Application File. Before dissemination, the texts will be sent by E-mail to the Coordinator for validation of their contents. In the absence of any response within 45 days, the texts will be considered validated.



5.12.3 Impact analysis

The Coordinator undertakes to compile—for subsequent posting on the ITMO Cancer Web site—an impact analysis summarising what the funded Project contributes to the fight against cancer.

5.13 Intellectual property

As funder and issuer of tenders for projects and grants, Inserm does not acquire any intellectual property rights. All intellectual property rights related to work on the Project and its results accrue to the Managing Body. If there is more than one Managing Body, they will have to agree among themselves about the allocation of intellectual property rights.

Compiling a consortium agreement is highly advisable if:

-  The overall total of the grant amounts to more than €250,000,
-  More than three partners are involved in the Project.

It is obligatory if a private-sector Managing Body becomes a partner in the Project.

5.14 Confidentiality

Inserm undertakes to preserve the confidentiality of all information acquired in the course of execution of the project, notably that contained in the Activity Report, hereafter referred to as the "Information". Inserm is not allowed to disclose anything at all in any form to any third party (apart from the Cancer Plan Steering Committee) without written permission from the Coordinator.

Nevertheless, Inserm will not be bound to secrecy for a specific point of information if it can prove that:

- ✚ The information is in the public domain without there having been infraction of the grant agreement or the Rules,
- ✚ The information was already known to Inserm on the date of signing of the agreement,
- ✚ The information becomes freely available from some other source which has the right to it.

5.15 Protection of personal data

Information of a personal nature collected in the Application File will be processed by computer to compile documents and help with the administrative and financial monitoring of Research Projects. In compliance with the Information Technology & Privacy Law of 6 January 1978 as amended in 2004, persons on whom data are collected have rights of access to, rectification of and deletion of information about themselves. These rights can be exercised by application to Inserm, Legal Affairs Department, 101 rue de Tolbiac - 75013 PARIS.

5.16 Settlement of disputes

For any conflict between Inserm and the Managing Body relating to interpretation or execution of the Granting Act, both parties undertake to bring their dispute to conciliators appointed by each of them (unless they can agree on a single conciliator) before recourse to any court.

The conciliator(s) will do all they can to settle the difficulties and bring the parties to amiable resolution within sixty (60) days of the date of their appointment.

In the absence of amiable resolution, the administrative judge will be convened to rule on the dispute related to application of the Granting Act.

5.17 Date of implementation of these Rules

These Rules come into force on the date of their publication and apply to grants allocated by Inserm in the framework of scheduling tenders for projects for 2015 and thereafter.






6 SUBMISSION PROCEDURE

The complete application file is submitted only in electronic format (no paper format is requested).

6.1 Application file

The application must include all elements that are required and needed for the scientific, technical and financial evaluation of the project. Applicants are recommended to produce a scientific and technical description of the project proposal in English. If the scientific and technical description is written in French, an English translation may be requested within a deadline compatible with the evaluation process milestones.

The applicant's file is composed of 5 elements:

-  The scientific file (download the scientific document to be used),
-  The financial file (download the Excel file to be used and upload an Excel version **AND a signed and stamped PDF version**). **The total budget requested should be coherent between the online Financial form, the financial annexe and the scientific file,**
-  PI and Co-PI Resumes (together in a single file) **using the template provided,**
-  The administrative forms (you have to fill it online on EVA3 in your personal space):
 - The online Administrative Form must be filled in for each participating team **whether funding is requested or not**
 - The Financial Form must be filled in for each team requesting funding
-  The bank information (Relevé d'Identité Bancaire).






All incomplete Projects will be considered administratively ineligible.

6.2 Electronic submission procedure

Website: <https://sp2013.inserm.fr/sites/eva/appels-a-projets/Pages/default.aspx>

This submission procedure from the EVA website of INSERM will include:

-  Identification of the candidate (surname, forename and e-mail),
-  The administrative section, as forms to be completed online,
-  Submission of the required documents by uploading (scientific dossier, financial appendices and CV of the project co-ordinator and heads of the participating groups).

Submission deadline: April 30th, 2019

Applicants are strongly advised not to wait until the proposal deadline to submit their project proposal.

7 PUBLICATION OF THE RESULTS

The list of projects financed will be published on the EVA website of INSERM. For these projects, the abstract will be published later, and each applicant will be contacted in order to confirm the content or provide a publishable version. Results will be communicated in writing to the coordinators.

8 CONTACTS

For further information, please contact:

- For scientific and technical aspects: plancancer.single-cell@inserm.fr
- For administrative and financial aspects: plancancer.daf@inserm.fr
- For problems relative to the electronic submission: eva@inserm.fr

Do not hesitate to consult the Candidate guide available on our EVA3 application.