IReSP
Institut pour la Recherche en Santé Publique

MINISTÈRE DE LA SANTÉ ET DE LA PRÉVENTION
Liberté
Égalité
Fraternité

Call for research projects

Effects of *in utero* exposure to antiseizure medications

Deadline for submission of projects: ***May 24th, 2023 - 3 p.m. (Paris time)***

Submission for applications: https://www.eva3.inserm.fr/

Presentation webinar online, followed by a discussion time: ***March 16th, 2023 de 10 a.m. - 12 p.m. (Paris time)***

Webinar registration here

Contents

1. Background and objectives

1.1. Background

Antiseizure medications (ASMs) such as sodium valproate and several other drugs have been widely prescribed to pregnant women in France and many other countries. Several studies suggested that children exposed *in utero* to specific ASMs have increased risks of malformations and neurodevelopmental disorders. This is clearly the case for sodium valproate (French commercial name Dépakine), while the level of evidence varies for the other ASMs. There is also concern regarding biological or health effects of these drugs in subsequent generations.

In this context, studies on the possible effects of ASMs prescribed during pregnancy in the generation exposed *in utero* and in the following ones, on their mechanisms of action, and the access to care for women with indications treated by ASMs and children exposed to ASMs *in utero* are scientifically warranted.

The French Institute for Public Health Research (IReSP)[1], whose main objective is to develop, structure, and promote public health research, has been entrusted by the French Ministry of Health (*Ministère de la Santé et de la Prévention*) to organise a research programme on ASMs and their health consequences on offspring. The research priorities of this programme have been defined by a group of experts[2] that identified four major areas:

Area 1: Teratogenic and developmental effects of ASMs in children exposed *in utero* with consideration of the specific effects of the most widely used ASMs.

Area 2: Generational[3] effects of sodium valproate and other ASMs.

Area 3: Toxicity mechanisms of ASMs in the context of *in utero* exposure.

Area 4: Care pathways and inequalities in access to care for women treated with ASMs and for *in utero* exposed children.

The expert group recognises that potential generational effects may be particularly difficult to untangle in humans, in particular when considering effects in the offspring of the *in utero* exposed generation. Therefore, animal studies (e.g., in rodents) are also encouraged to assess this phenomenon.

An international scientific committee with multidisciplinary expertise relevant to this research programme has been set up to ensure its oversight. The scientific committee proposed to launch two related calls:

1. A *Call for Research Projects* on the effects of *in utero* exposure to ASMs, covering the four areas above;
2. A *Call for Expression of Interest* aimed at structuring *ad hoc* research consortia to address a part of Area 2, human studies on intergenerational effects of *in utero* exposure to ASMs in the children and grandchildren of treated women; for this please refer to https://iresp.net/appel_a_projets/appel-a-manifestation-dinteret-2023-antiepileptiques/

The present *Call for Research Projects* will provide financial support for selected research projects in the areas of interest specified in this text. In contrast, the *Call for Expression of Interest* is a two-step process that will first allow selection of teams with complementary expertise. In the second phase, and with the support of IReSP, these teams will co-construct a research project that will best meet the identified needs in Area 2 and that will then be evaluated for funding support.

[1] IReSP is a Scientific Interest Group (GIS) hosted by The French National Institute of Health and Medical Research (Inserm)

[2] https://www.inserm.fr/rapport/rapport-sur-les-pistes-de-recherche-concernant-les-effets-a-court-et-long-termes-de-lexposition-intra-uterine-a-la-depakine-et-autres-antiepileptiques/

[3] In the context of this call, we refer to *generational effects* as encompassing intergenerational (F0 generation women treated with ASMs during pregnancy, F1 generation children exposed in utero to ASMs, and F2 generation grand-children of women treated with ASMs) and transgenerational (F3 generation great-grandchildren of women treated with ASMs).

1.2. Objectives

This call for research projects aims to address issues relative to ASMs exposure during pregnancy and its health effects. All ASMs can be considered, with particular attention given to those that are the most widely used.

The specific objective of this call for research projects is to support research and produce knowledge regarding the four areas described above, which are:

Area 1: Teratogenic and developmental effects of ASMs in children exposed *in utero* (limited to humans).

Area 2: Generational effects of ASMs.

Area 3: Toxicity mechanisms of ASMs in the context of *in utero* exposure.

Area 4: Care pathways and inequalities in access to care for women treated with ASMs and for children exposed *in utero*.

The call is multidisciplinary and is preferentially open to disciplines such as epidemiology and pharmacoepidemiology, public health, neurobiology and developmental neurobiology, neuropsychology, clinical and general medicine, dysmorphology, molecular genetics and epigenetics, toxicology, pharmacology, imaging, exposure science, sociology of health, ethics, and philosophy. This list is not exhaustive and the call for proposals is also open to all other disciplines able to address the areas of interest.

2. Modality of support

This call aims to support research projects and pilot research projects, which may bring together several complementary teams, including research teams based outside France[4].

Research projects: These are projects with an advanced design, founded on a strong methodological approach and successful partnerships, based for example on data from pilot studies, emerging projects, or feasibility evaluations.

Duration: up to 36 months.

Budget: €40,000 to €800,000. This maximum amount can be exceeded exceptionally, for especially well-evaluated projects.

Pilot research projects: This modality is aimed for small-scale preliminary studies with a view to determining feasibility, time frames, costs, and risks before conducting a full-scale project.

Duration: 12 to 24 months.

Budget: up to €100,000 maximum.

3. Scope

A special attention will be paid to project feasibility and power calculations for all study areas.

Research area 1: Teratogenic and developmental effects of ASMs on children exposed *in utero* (limited to humans)

The data currently available on the teratogenic and neurodevelopmental disorders associated with ASMs taken during pregnancy strongly vary between ASMs.

For sodium valproate, the teratogenic and neurodevelopmental risks in children born to women treated during pregnancy are proven. For topiramate, carbamazepine, phenobarbital and phenytoin, an increased risk of malformations and/or neurodevelopmental disorders has been at least partially demonstrated but still needs to be explored.

However, for a number of ASMs, the data are lacking to conclude that a risk exists. Further research is needed, especially for ASMs that are commonly used during pregnancy but with limited or extremely limited data regarding risks of congenital anomalies and/or

[4] However, the project coordinator must reside in France and belong to a French affiliated organisation.

neurodevelopmental disorders, i.e. gabapentin, lacosamide, pregabalin, oxcarbazepine, zonisamide, etc.

The objective of this research area is to improve quantification and characterisation of the risks of birth defects and neurodevelopmental disorders associated with the various ASMs – especially those commonly used in women of childbearing age and/or during pregnancy – used alone or in combination with other ASMs.

Methodological approaches needed

The research should be based on epidemiological studies that use existing medical and administrative databases and/or existing cohorts. Studies on large populations, based on existing data sources, are crucial to investigate signals and clarify the teratogenic and neurodevelopmental risks associated with *in utero* exposure to these ASMs. Data sources may include:

- Existing large databases with routinely collected data: National Health Data Systems such as the French SNDS[5], hospital data warehouses, registries (e.g. of congenital anomalies or of childhood disabilities), and other potential existing data sources.
- New or existing cohort studies of women recruited in the periconceptional period with good quality information on medication consumption and with a follow-up allowing identification of congenital anomalies: an active monitoring of pregnancy outcomes and of the neonate for at least the first year of life, for neurodevelopmental disorders, a follow-up with specific evaluations during childhood and/or an enrichment by health or administrative databases.

Note that we are aware of an ongoing research project, coordinated by the EPI-PHARE scientific interest group, that relies on the French SNDS and addresses the teratogenicity and effects of ASMs on children exposed *in utero*. Projects using alternative approaches and relying on sources other than solely the SNDS will be given priority.

Research Area 2: Generational effects of ASMs

The objective of this research area is to evaluate the intergenerational and transgenerational risk of neurodevelopmental disorders and/or congenital abnormalities or pathologies following *in utero* exposure to valproic acid and other ASMs such as carbamazepine and topiramate in animals and humans.

Methodological approaches needed

Are expected: studies using animal models, such as rodents (mice or rats), that involve exposure during critical periods of gestation, possibly at doses comparable or equivalent to those used in humans, are expected. Ideally, outbreed lines should be used to avoid inbreeding depression, phenomenon characterised by reduced survival and fertility of offspring of related individuals, and that has been attributed to both genetic and epigenetic. At least the exposed F0 female generation, F1 generation (offspring), F2 generation (grand-offspring), and transgenerational F3 generation (great-grand offspring) should be analysed, to assess the intergenerational and transgenerational (no direct exposure) impacts of ASMs. Physiology and pathology should be assessed in the young adult (i.e., 90-day age for rodents) and older adult (i.e., 1 year for rodents) animals. In addition to systemic congenital disease assessment (e.g., gonads, reproductive tract, kidney, etc.), neurological testing could be assessed for anxiety, memory, and other neurodevelopmental and neurobehavioral disorders during postnatal days 30, 90, and 1 year for rodents.

In addition, or as an alternative to the animal studies, epidemiological studies of the children (and, if possible, grandchildren) of women exposed to ASMs during pregnancy may be considered. Non-exposed and exposed populations will be needed to assess pathology and

[5] *Système National des Données de Santé* (SNDS) (https://www.snds.gouv.fr/SNDS/Accueil) is a medical administrative database covering all French population with exhaustive, comprehensive information on reimbursement and recourse to healthcare and hospitalization and clinical data, since 2006.

neurodevelopmental abnormalities in the children and grandchildren as young adults and/or older adults. Epidemiological studies may be based on the results of animal studies concerning the pathologies and periods of development to be taken into account.

Note that teams interested in the co-construction of a research project in humans related to this area should refer to the accompanying call for expression of interest (https://iresp.net/appel_a_projets/appel-a-manifestation-dinteret-2023-antiepileptiques/)

Research Area 3: Toxicity mechanisms of ASMs

The objective of this research area is to establish the cellular and molecular (including epigenetic) mechanisms by which the most commonly used ASMs in pregnancy are likely to disrupt organogenesis and development or induce specific diseases.

Methodological approaches needed

Are expected: comparative experimental studies with simultaneous (head-to-head) comparison of different common ASMs using validated and standardised protocols. Such comparisons might involve, for example, screening for specific mechanisms (e.g., calcium mobilization) and downstream transcriptional events in purified populations of cultured cells. Since each cell type has distinct cell-specific epigenetics, purified cells for culture studies are optimal. Although classic toxicology screens for the different ASMs will likely have been done as part of the investigational new drug submission, this will have to be verified for each drug and expanded to consider epigenetics and metabolites.

Studies of *in utero* exposure to different doses of ASMs at different periods of development in an animal (mice or rat models) can be used to assess the most impactful exposure periods and doses. Purified cell populations of placental tissue (e.g., trophoblasts) and embryonic tissue (e.g., skin) can be used to study impacts on gene expression and epigenetics (e.g., DNA methylation). Studies on epigenetic programming will be important to assess possible long-term developmental impacts on individuals later in life. Since ASMs possibly disrupt synaptic transmission, outcome measures in adults could consider the assessment of cognition and social interactions.

Note that the above-mentioned methodological approaches are examples and may differ depending on the target of research.

Research Area 4: Care pathways and inequalities in care access to women treated with ASMs and for children exposed *in utero*.

In France, as possibly in other countries, the care pathway for patients with epilepsy is insufficiently organised, especially during the crucial period of pregnancy and in women reaching childbearing age, as well as for children exposed to ASMs *in utero*.

The objective of this research area is to analyse the existing care pathways and inequalities in care access (follow-up and management). Research priorities need to analyse the care organisation, the disparities in access to care, whether social or geographic, the crucial period of the transition between adolescence and adulthood in women with epilepsy, as well as the perceptions, knowledge, and practices of practitioners and patients. They could also treat ethical issues related to consideration of risks associated with pregnancy in women.

Methodological approaches may differ depending on the target of research and resulting information delivered to address these questions. Finally, combinations of data collected specifically for research (cohorts/randomised trials) matched with the SNDS, practice studies, longitudinal approaches, and qualitative studies with patients and healthcare professionals should be considered. In addition, interventional research will also be possible to assess interventions aimed at improving care pathways and reducing inequalities in care access.

4. Schedule

The schedule for this call for research projects is as follows:

- Launch of the call for research projects: **February 20th, 2023.**
- Webinar presentation: **March 16th, 2023.**
- Deadline for electronic submission of the application: **May 24th, 2023 at 3 pm (Paris time).**
- Evaluation of the call for proposal: from **June to November 2023.**
- Provisional date of announcement of results: **December 2023**.

5. Project selection procedure and announcement of results

5.1. Scientific evaluation committee

To evaluate the submitted proposals, IReSP convenes an international scientific evaluation committee whose members are selected for their expertise.

Inserm and IReSP have established a process in terms of professional ethics and transparency of interests. The scientific evaluation committee commits to respecting the professional ethics provisions of the two institutes.

All members of the scientific evaluation committee are required to sign a non-disclosure and conflict of interest statement outlining their direct and indirect interests relating to each project submitted to IReSP and relating to project coordinators or members of a project team.

The composition of each scientific evaluation committee is confidential and will be published at the end of the evaluation process of the call for proposals.

5.2. Stages in the selection procedure

The selection procedure features several stages based on complete applications:

- **Stage 1: Admissibility and eligibility.** IReSP examines all applications according to the admissibility and administrative eligibility criteria, the conditions of which are defined below. The scientific eligibility is carried out with a part of the scientific evaluation committee.
- **Stage 2: External scientific evaluation**: external evaluators, international and French, are called upon to provide an evaluation of the eligible and admissible projects. Two external evaluators examine each project. These independent experts are chosen for their scientific excellence, in compliance with ethical and deontological rules (notably by the signature of a declaration of confidentiality and non-conflict of interest by each expert).
- **Stage 3: Scientific evaluation by the members of the scientific evaluation committee**. Each project is then evaluated by two members of the scientific evaluation committee, who draws on the external evaluation. The scientific evaluation committee then discusses the quality of the projects together and proposes a list of projects to be funded.
- **Stage 4: Notice of opportunity.** Based on the ranking proposed by the scientific evaluation committee, the *Ministry of Health and Prevention* decides on this ranking through a notice of opportunity.
- **Stage 5: Final decision by IReSP.**

5.2.1. Admissibility criteria

Applications must be:

- Submitted before the deadline **May 24th, 2023 - 3 p.m. (Paris time)**;
- In electronic format **only** via the EVA3 platform: https://www.eva3.inserm.fr/ (see 9. for specific information)**.**

- **Written in English**
- **Complete:** Electronic submission application must contain all required information (Word scientific document in Word format and financial document in Excel format).
- **Signed:** electronic signatures are accepted and all signatures must appear in the Word application.

5.2.2. Eligibility criteria

To be **administratively eligible**, projects must satisfy the administrative and financial conditions of this call. In particular, it is recalled that:

1. The scientific project coordinator must be resident in France and must belong to a French organisation (see 6.1);
2. The scientific project coordinator must not be a member of the scientific evaluation committee, the international scientific committee, or a stakeholder in charge of this call;
3. The structures receiving the funds must be eligible (see 6.3);
4. The project must last a maximum of 36 months for full research projects and 24 months for pilot projects;
5. The number of teams participating to a project is limited to 10 (including the coordinator's team) applying or not for funding;
6. If the project is already in progress or funded by other public bodies, the same objectives can be co-funded but the same activities will not be funded twice, and this will need to be clearly established and justified to receive funding from IReSP;
7. International collaborations and non-French teams are eligible for funding only if they are coordinated and associated with a French team and will be funded at a maximum of 35% of the total amount of funding requested.

To be **scientifically eligible**, projects must meet the following conditions:

1. The project must fulfill the scope and objectives of this call for research projects;
2. The project may cover one or several axes of this call for research projects.

5.2.3. Scientific evaluation criteria

Applications that meet the eligibility criteria will be evaluated based on the following scientific evaluation criteria:

Scientific quality:

- Excellence in relation to current scientific knowledge;
- Position of the proposal in relation to the national and international context;
- Relevance and originality of the proposal;
- Consistency with the target subject areas;
- Clarity of the objectives.

Coordinator and partner teams:

- Quality and synergy of the partnership between researchers and field players;
- Quality of the teams involved (skills, experience, complementarity profiles, etc.);
- Added value of foreign teams.

Methodology and feasibility:

- Methodological quality and relevance of the planned technologies;
- Suitability and justification of proposed schedule with regard to the project's objectives;

- Feasibility of the research (access to data, schedule for completing project tasks, detailed programme, deliverables, compliance with ethical rules and regulatory requirements, status of authorisation requests, declaration of access to databases or to cohorts, etc.);
- Technical, financial and legal-administrative feasibility (budget in line with the application, compatibility of the funding obtained through the call for proposal with any other funding that the structure could or will receive).

Impact of the proposal:

- Scientific, technical, medical, social, or public health impact;
- Innovative characteristics.

5.2.4. Notice of opportunity

Based on the ranking proposed by the scientific evaluation committee, the *French Ministry of Health and Prevention* give an opinion through a notice of opportunity, mainly concerning projects involving foreign teams with regard to the added value of these teams in the projects.

5.2.5. Final decision

The results of the evaluation will be emailed to the project coordinators. For the selected projects, IReSP will send a letter to the project coordinator as well as to the legal representative of the organisations receiving the funding.

The list of selected projects will be published on the IReSP website.

In addition, IReSP reserves the right to publish on its website the abstracts of submitted projects funded.

6. Teams, coordinators, affiliated organisations and commitments

6.1. Project scientific coordinator

The team coordinating the project will be team 1, and its affiliated organisation must be French and eligible for this status (see 6.3).

Each submitted project must designate a scientific coordinator. Scientific coordinators are natural persons and are responsible for achieving the project's scientific deliverables. They act as the principal manager of the project and the point of contact for IReSP. **Project coordinators alone are authorised to submit the application in their name.** Scientific coordinators must dedicate **at least 10% of their research time** to the project.

As the project leader, coordinators will be designated in the funding grant agreement if applicable. In addition to his/her scientific and technical role, the coordinator is responsible for the entire deployment of the project and for:

- Establishing the collaborative arrangements between the participating teams;
- Producing the required documents (progress reports, interim and final reports, summary records, scientific and financial reports, etc.), holding meetings, moving the project forward, and disclosing the results.

Only **one** scientific coordinator may act as the point of contact for the submitted project. Scientific coordinators must not be scientific committee nor scientific evaluation committee members involved in the call for proposals. Project scientific coordinator **must reside in France**, hold a research doctorate/ PhD[6], and be involved in a research activity.

In addition, project scientific coordinators must:

- Be a permanent staff member (permanent post-holder in the civil service or on an open-ended contract), or

[6] Holders of a PhD or a state diploma of doctor of medicine or pharmacy with a research activity in France can also be coordinators.

- Hold a fixed-term contract, if the contract covers the entire project duration in one of the eligible structures (see 6.3), or
- Provide a binding offer of employment issued by the employer *when submitting the application* that covers the entire project duration.

Chair holders and postdoctoral students may also be project coordinators. Doctoral students, emeritus researchers, or retirees may not be project coordinators. The coordinating team may form a research consortium with partner teams.

6.2. Partners teams

The number of partner teams participating in the project, **whether applying for funding or not**, is limited to nine. The number of people involved in each team is not limited. Each partner team must designate a scientific leader. The scientific leader's affiliated organisation must be eligible for one of the statuses described below (see 6.3).

The research consortium must ensure that the application and financial appendix specifies all the partner teams involved in the project and their composition, **irrespective of whether they are applying for funding.**

Regarding the participation of foreign teams, we would like to draw your attention to the fact that the scientific evaluation committee, during its evaluation, and then the *French Ministry of Health and Prevention*, during its notice of opportunity, will look carefully at the added value provided by these teams.

Distinction between partner teams and service providers

- *The **partner team** must be involved in building and developing the research project. As such, it can receive and use project-related credits more easily. However, the partner team must achieve the defined objectives, otherwise it could be liable for reimbursing all or part of the sum awarded.*
- *The **service provider** is required to perform a specific and occasional task during the project, which must be duly justified in the application (application and budget appendix). If applicable, the affiliated organisation must ensure compliance with public procurement rules in accordance with its articles of association. The service provider cannot be responsible for the non-achievement of the objectives as a whole; however, it is bound by an obligation to result with regard to the specific task for which it has been asked.*

6.3. Affiliated organisations

For each project submitted, the teams involved must designate their affiliated organisation, irrespective of whether it is the recipient of the funding. The organisations to which the scientific coordinator and partner teams belong must comply with the following conditions:

Legal status (in accordance with the organisation's articles of association or founding texts)	**Coordinator** Fundable organisation	**Partner teams:** Fundable organisations	**Partner teams:** Organisations not applying for funding
French public establishments			
Public establishments vested with a research mission: EPSCPs (public scientific, cultural and professional establishments e.g., universities, academia, etc.), EPSTs (public scientific and technological establishments- e.g., Inserm, CNRS, INRAE, etc.), certain public industrial and commercial establishments (EPICs) or public administrative establishments (EPAs), and	YES	YES	YES

public healthcare facilities (teaching hospitals, medical centers, general hospitals, etc.)			
Public interest groups vested with a research mission	YES	YES	YES
Non-French Public establishments			
Foreign teams	NO	YES*	YES
Private establishments			
Private non-profit healthcare facilities vested with a research mission	YES	YES	YES
Research foundations (vested with a research mission laid down in their articles of association)	YES	YES	YES
State-approved public-interest foundations (Institut Pasteur, Institut Curie, etc.)	YES	YES	YES
Scientific cooperation foundations (teaching hospital institutes, etc.)	YES	YES	YES
Other foundations	NO	YES	YES
Associations (see comment below)	NO	YES**	YES
International organisations applying on behalf of research teams based in France	NO	YES	YES
Self-employed healthcare professionals (see comment below)	NO	NO	YES

**International collaborations (non-French teams) are encouraged. However, to be eligible for funding, non-French teams must be associated with a French team, and cannot be the coordinating team. They will be funded up to a maximum of 35% of the total amount of funding and will be considered as privately owned partner for the financial rules of the call.*

***All associations applying for funding must ensure that their application contains their articles of association, profit and loss statements for the last financial year, an organisation chart, and confirmation of their financial resources from their bank within the previous three months. All the said documents will be examined to confirm that the project is eligible from an administrative point of view.*

For each project, the funding will be paid to one structure that will be responsible for distributing the funds to the other structures for the benefit of the teams taking part in the project. This coordinating structure receiving the funding must have a public accountant. This recipient structure shall also be responsible for justifying the expenses to the body that allocates the funding.

Note: privately owned partners and healthcare professionals

- An **eligible privately owned partner** may receive financial support only **up to 80%** of the total budget requested for the project.
- Self-employed healthcare professionals are not directly eligible for funding. However, two possibilities are available:
    - Funding as service providers (see comment under 6.2);
    - Affiliation with a structure that is eligible for funding (see table above).

6.4. Commitments

Project participants must agree to comply with the funding rules by signing the commitments specified in the application.

For the project coordinator team: signatures (which may be electronic) are required from the project coordinator, the director of the laboratory with which the coordinator is affiliated (or the director of the coordinator's structure), and the lawful representative of the affiliated organisation.

For the project partner teams applying for funding: signatures (which may be electronic) are only required from the team leader and the lawful representative of their affiliated organisation.

In case of partner teams not applying for funding, only the team leader is required to sign.

7. Financial rules and deliverables

Please read carefully the recommendations below and the budget appendix, which will help you to establish your budget and to fill in the budget appendix correctly.

Funding may cover all or part of the project budget. Each team is asked to contact its managing organisation to ensure the coherence of the financial package before submitting the application and closing the call for research projects.

The legal representative of the managing body of each team applying or not for funding **must sign** the application budget appendix.

7.1. General recommendations for completing the budget appendix

In the budget appendix (Excel format), **only the blue cells must be filled in**.

All amounts must be entered in euros and without additional tax, non-recoverable VAT, if applicable. It is requested, to fill in this budget appendix by rounding the amounts to the nearest euro.

The budget appendix has several sheets:

1. **The notice**: this should be read carefully before filling in the other sheets.
2. **Sheet "Team" (from "A-Team 1" to "J-Team 10"):** all teams, including those not applying for funding, must fill in the relevant tab.
3. **Sheet " K - Annual distribution":** the funding requested must be broken down into annual distribution for the implementation of the project. This distribution is done by calendar year.
4. **Sheet "L - Summary sheet":** this tab is filled in automatically from the data provided in the other tabs. Please do not modify.

Please note:

- To guarantee the integrity of all automatically calculated data, neither the structure of the file (no deletion or addition of tabs), nor the names of the tabs must be modified. **Any request to modify the Excel file must therefore be submitted to IReSP** (e.g. additional lines for permanent or fixed-term staff, etc.);
- The coordinator's team must be identified as team n°1;
- The numbering of the teams must be the same between the budget appendix (Excel file) and the application form (Word file).

7.2. General provisions for funding

The costs attributable to the research project must be strictly related to its implementation, which **excludes any profit margin**. Co-funding of projects is authorised, as a complement to funding obtained elsewhere. However, funding allocated here may not cover expenses financed elsewhere.

Expenses included in the requested budget may only correspond to expenses incurred after the project start date and carried out before the end date of the project.

The managing organisation may deduct overheads, as set out in the budget appendix, up to 13% maximum of the amount of eligible expenses calculated excluding overheads.

To estimate the total budget, it will be necessary to take into account the expenses related to the permanent staff involved in the project but also the expenses related to the future recruitment of research staff.

Equipment purchases, transport and accommodation costs, outsourcing costs and management costs must also be taken into account. The purchase of computer hardware and software is only allowed if it is essential for the realisation of the project and its use is precisely justified in the scientific description of the project highlighting its specific properties. The aid granted is not intended to equip the staff assigned to the project with standard office equipment. IReSP reserves the right to refuse the request if it is not sufficiently justified.

The coordinator must refer to section 2 to know the minimum and maximum amounts of funding according to the support modality.

7.2.1. Personnel expenses

The funding requested for personnel may not exceed 85% of the total amount of the project.

Support and administrative functions are not eligible for funding, nor the expenses that would be attached to these functions (office equipment, mission, etc.). However, scientific profiles such as grant officers or lab managers are eligible.

The funding for trainees, masters, doctoral and post-doctoral students is allowed. Doctoral students and post-doctoral fellows must be mentioned:

- in "Temporary staff (CDD) for which funding is requested (a2)(1)" if the organisation is a public law institution, or;
- in "Fixed-term staff for which funding is requested (a2)(2)" if the organisation is a private law institution (e.g. research foundation).

Internships for which a bonus is paid must be included in the expense related to "purchase of small materials, consumables, operations". The number of trainees and their identity, if known, must be indicated in the justification (h) in the section "Details of expenses for the purchase of small equipment, consumables and operations".

A French team cannot support fixed-term contracts (post-doctoral fellows, doctoral students, etc.) or trainees working in foreign laboratories, unless this stay does not exceed one third of the project's total duration.

For the funding of eligible private legal entities: the funding of private legal entities (see 6.3) will be granted up to 80% of the total cost of the project. Therefore, each private law organisation will have to demonstrate that it can cover 20% of the total cost of the research project from its own resources, failing which its research project will not be selected.

7.2.2. Payment of the grant

The managing body of IReSP is Inserm. Inserm will be the referent for the implementation of the grant awarding acts, the payment of the grant, the administrative and financial follow-up of the projects. Inserm makes payments to the scientific coordinator's management body.

The scientific coordinators may be contacted by IReSP or Inserm and asked to update or supplement the following documents required for allocation of the funding:

- the detailed budget;
- the commitments of the legal representative of the coordinating structure receiving the funding;
- the additional documents required for the funding of private non-profit bodies (signed copies of the up-to-date statutes, copy of the publication in the French Official Gazette of the declaration of the body's constitution, activity report, list of members of the director board and executive committee, and extract from the official report approving the accounts of the previous closed financial year).

The funding will be paid on the project start date determined by the project coordinators. This date must be set within six months of the announcement of the results of the call for projects. It must also be later than the date on which the funding decision is issued.

Insofar as the same project involves several partner teams, payment agreements must be drawn up between the coordinator's management body and the management bodies of the partner teams receiving funding. Any modification of the budgetary appendix after the notification of funding or after the signature of the agreement **must be requested by email to IReSP and Inserm**.

At the end of the grant, the coordinator must reimburse Inserm for any unspent amounts.

8. Project monitoring deliverables and communication

8.1. Project monitoring deliverables

The coordinator of the funded project is required to provide several scientific and financial reports, including a progress report at 6 months, a mid-term report and a final report depending on the duration of the project (https://iresp.net/financements/suivi-des-projets/). These reports include a scientific part to report on the results of the research and including an executive summary; and a financial part to list the expenses mandated to date.

The list of publications and any other project dissemination and communication activities must also be provided.

All the documents to be provided and the date of their submission will be specified in the grant awarding act.

8.2. Publication and communication

The partners undertake to mention the support of IReSP and the French Ministry of Health, in publications and communications concerning the project.

They must inform IReSP of publications by email within two weeks of their publication, even after the end of the funding agreement, and register the studies and results according to the procedures specified in the agreement, in coherence with IReSP commitments to open science, transparency and research integrity.

IReSP does not acquire any intellectual property rights only from financing calls for proposals and providing funding. The results of these projects belong, according to the regulations, either to the researchers who generated them, or to their employing institutions, or to the parent institutions of the research teams involved.

Drafting a consortium agreement is strongly recommended when:

- The total amount of the funding is more than € 250,000;
- More than three structures are involved in the project.

Drafting of a consortium agreement is mandatory in the case of international collaboration involving non-French teams in the project.

IReSP leaves it entirely up to the scientific leaders to publish, in compliance with the rules applicable to them, knowledge produced within the framework of projects supported under a call for projects. In the framework of the implementation of the 2nd national plan for Open Science, the grant recipient organisation and the project coordinator undertake, in case of funding, to:

- Give priority to the publication of scientific articles resulting from funded research projects in open access journals or books. Failing this, the beneficiary and the teams participating in the project undertake to deposit in a public open archive such as HAL. Article 30 of the Law for a Digital Republic sets a maximum embargo period:
    - 6 months for publications in the field of science, technology and medicine (STM);

- 12 months for publications in the field of humanities and social sciences (SHS). Dissemination may take place without delay or within a shorter embargo period than the above if the publisher so authorises.

In principle, the structure in charge of coordinating the project is tasked with drafting the consortium agreement.

9. General recommendations for electronic submission

The full application must be **submitted online in electronic format only, before the deadline.**

Finalised application must contain all the elements necessary for the scientific and technical evaluation of the project (application form and financial appendix). Finalised application shall be submitted in electronic form only (online).

Required documents must be uploaded to the EVA3 platform: https://eva3-accueil.inserm.fr.

Instructions for applicants:

- **Create/activate EVA3 account:** to log in, use your reference email address as your login on the EVA3 platform login page (https://www.eva3.inserm.fr/).
- If you have not yet registered, create your account.
- If you already have an account but have forgotten your password, click on “Forgot password?” and follow the instructions.

Application submission: all applications **must be submitted only under the coordinator’s name and contact details**. Applications submitted under another name/email address shall be **inadmissible**.

Applications:

One person only submits each application. If several researchers from the same team submit an application, one of the researchers should be designated as the contact.

The applicant logs into his or her account on the EVA3 platform, and:

1. Enters the data requested online.
2. Downloads the application document templates (Word scientific file and Excel financial appendix).
3. Submits the required documents **completed and signed**.
4. Validation/submission: the final validation generates an email acknowledging receipt and confirming file submission. **N.B.: after validation, you will no longer be able to return to the contents of your file.**

10. Contact

For information of a **scientific nature**, please contact:

- Sandrine Saillet: sandrine.saillet@inserm.fr

For **administrative and financial** aspects:

- IReSP: iresp.daf@inserm.fr

For **technical aspects**:

- concerning EVA3: eva@inserm.fr