Call for expression of interest

To co-construct a research project on the intergenerational effects of *in utero* exposure to antiseizure medications in humans

Deadline for submission of projects: ***May 10th, 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

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1. Background and objectives

1.1. Background

Antiseizure medications (ASMs) such as sodium valproate and many other drugs have been widely prescribed to pregnant women in France and many other countries. Several studies suggested that children exposed *in utero* to 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 the subsequent generations.

In this context, studies on the possible effects of ASMs prescribed during pregnancy in the generation exposed *in utero* and the following ones, on their mechanisms of action, and on 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 all four areas above; for this please refer to https://iresp.net/appel_a_projets/appel-a-projets-de-recherche-2023-antiepileptiques/
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.

The *Call for Research Projects* will provide financial support for selected research projects in the areas of interest. In contrast, the present ***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 best meets 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 (women treated with ASMs during pregnancy exposed F0 generation, children exposed *in utero* to ASMs F1 generation and grandchildren of women treated with ASMs F2 generation) and transgenerational effects (great-grandchildren of women treated with ASMs F3 generation).

1.2. Objectives and overview of the process

The objective of this call for expression of interest is to **support researchers in the co-construction of a project** addressing the question of the potential intergenerational effects in humans of ASMs used during pregnancy. It aims to address the challenging questions of the intergenerational effects of ASMs in children (exposed *in utero*) and grandchildren of women treated with ASMs during pregnancy. More specifically, the purpose of this call for expression of interest is to generate, identify, co-build, and fund a **joint project** that will best meet the identified needs.

The first stage of this call aims to gather complementary teams whose selection will be based on a letter of expression of interest. The teams selected at the end of this first stage will then work together to jointly develop a finalised research project, and IReSP will help organise seminars to support the participants in this co-construction process. At the end of this phase, the resulting submitted project will be evaluated by the international scientific evaluation committee to reach a decision about funding.

2. Scope

This multidisciplinary call for expressions of interest is open to all disciplines that can contribute to the above objectives.

Studies in animals have suggested intergenerational effects of valproate in offspring of mothers exposed to ASMs during pregnancy. Preliminary observations of malformations and/or neurodevelopmental disorders in grandchildren of women that used valproate during pregnancy have also been reported. However, to date, there have been very few large-scale investigations of intergenerational effects in humans, nor transgenerational impacts in animal studies.

This call seeks applications from investigators able to develop an epidemiological study in populations that would allow assessment of intergenerational risk of ASMs[4], be it based on existing data or data not yet or only partly gathered (e.g., records of medications used in pregnancy, maternal indication for use of ASMs, maternal comorbidity, etc.). The study design should cover a time period long enough to allow the study of intergenerational effects, e.g. health effects in children and grandchildren born from mothers exposed to ASMs during pregnancy and should also allow for an accurate assessment of the use of ASMs. Well-documented power analyses/sample size calculations and feasibility issues will be essential.

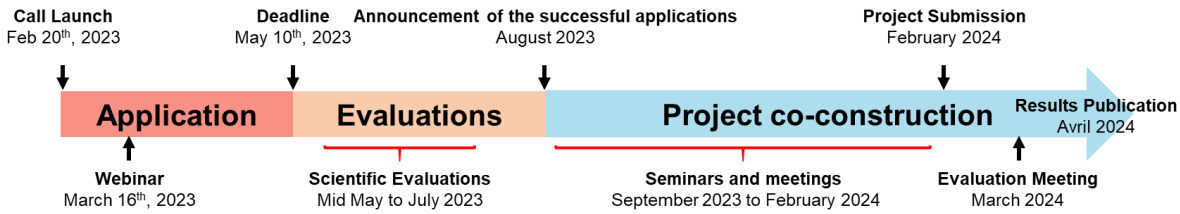
International collaborations with scientific teams from countries that have registers or databases that do not exist in France or that are complementary (e.g. with data covering long periods of time or on the use of prescriptions) and can be linked are encouraged.

3. Schedule

The schedule for this call for manifestation of interest is as follows:

- Launch of the call for expression of interest: **February 20th, 2023.**
- Webinar presentation: **March 16th, 2023.**
- Deadline for electronic submission (letter of expression of interest): **May 10th, 2023 at 3 p.m. (Paris time).**
- Announcement date of the successful applications: **August 2023.**
- Project co-construction: Seminars and meetings **from September 2023 to February 2024**.
- Submission of the complete co-constructed project: **February 2024.**
- Provisional date of results publication: **April 2024.**

[4] This may also apply to benzodiazepines if they are used as ASMs.



4. Teams' selection and co-construction processes

4.1. Overall organisation of the call for expression of interest

This programme will take place in several stages:

- application of research teams ("letter of expression of interest");
- selection of teams;
- co-construction of the project by the selected teams;
- submission and evaluation of the complete project;
- funding decision.

A scientific evaluation committee will follow the programme. Its mission is to select the letters of expression of interest, to make recommendations as to the directions of the programme, to advise any possible convergence between the teams for the constitution of the working groups and to evaluate the finalised co-constructed scientific project. The scientific evaluation committee is composed of international experts.

IReSP will coordinate the call for expression of interest.

4.2. Stage 1: Teams selection

This call for expression of interest is open to all eligible teams (see 5.2).

For stage 1, a letter of expression of interest must be written in English and submitted before **May 10th, 2023** (the application file is available on the IReSP website (https://iresp.net/appel_a_projets/appel-a-manifestation-dinteret-2023-antiepileptiques/). The scientific evaluation committee will evaluate applications and the selected teams will be invited to be part of the co-construction programme.

Applications are expected to come mainly from individual teams. To ensure the complementarity of the consortium that will be selected for the co-construction process, teams coming from different fields and disciplines, including international foreign research teams, are encouraged to apply.

4.3. Stage 2: Co-construction of research project

During the following co-construction phase, several seminars will be organised to support the participants and foster the sharing of knowledge, in addition to informal communications and exchanges. The indicative content of these seminars could include:

- A first seminar allowing the selected teams to get to know each other, present their ideas, and delineate challenges, pitfalls and relevant approaches; identification of a coordinating team and project leader;
- A seminar to progress in the development of the proposal;
- A presentation of the pre-project can be organised during the project co-construction;
- Meeting(s) to finalise the project conception.

During the co-construction programme, financial support will be provided to participants (travel and meeting costs), as well as organisational and material support.

4.4. Submission and evaluation of the complete project for funding

The complete project will be submitted by the consortium and evaluated by the scientific evaluation committee, possibly after an oral presentation.

5. Terms and conditions of participation

5.1. Eligible terms

For letters of expression of interest: Teams with a managing body eligible for funding (see 5.2) are eligible.

For the final research project: The co-construct project will involve several teams from different research units, fields and/or organisations (see 5.2). The establishment of a consortium is strongly recommended to facilitate the internal organisation of the research project.

5.2. Affiliated organisation

The funding of the complete final research project will concern legal persons established in France and outside of France.

Teams involved must designate their affiliated organisation. The affiliated organisations **must comply with the following conditions**:

Legal status (in accordance with the organisation's articles of association or founding texts)	**Candidate** Fundable organisation
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- Inserm, CNRS, INRAE, etc.), certain public industrial and commercial establishments (EPICs) or public administrative establishments (EPAs), and public healthcare facilities (teaching hospitals, medical centers, general hospitals, etc.)	YES
Public interest groups vested with a research mission	YES
Non-French public establishments	
Foreign research teams	YES*
Private establishments	
Private non-profit healthcare facilities vested with a research mission	YES
Research foundations (vested with a research mission laid down in their articles of association)	YES
Scientific cooperation foundations (teaching hospital institutes, etc.)	YES
International organisations applying on behalf of research teams based in France	YES

*International non-French teams are encouraged to apply. However, they will be funded at a maximum of 35% of the total amount of funding and could not be the coordinating team.

For the co-constructed project, the funding will be paid to the coordinating team organisation, which will be responsible for distributing the funds to the other structures for the benefit of the teams participating in the project. This coordinating structure receiving the funding must have a public accountant. This recipient structure shall also be responsible for justifying the expenditure to the body that allocates the funding.

Note: An **eligible privately owned partner** can only receive financial support only **up to 80%** of the total budget requested for the project.

6. Selection and evaluation procedure

6.1. Scientific evaluation committee

Inserm and IReSP have established a system in terms of professional ethics and transparency of interests. The members of the scientific evaluation committee commits to respecting the professional ethics provisions of the two institutes and are required to sign a non-disclosure and conflict of interest statement outlining their direct and indirect interests relating to each project submitted application to IReSP relating to project coordinators or members of teams applying.

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

6.2. Selection and evaluation process

To evaluate the submitted letters of expression of interest, IReSP will examine the admissibility regarding the eligibility criteria. These letters will then be submitted for evaluation to the above-mentioned scientific evaluation committee whose members are internationally renowned for their expertise.

6.3. Admissibility and eligibility criteria of the letter of expression of interest

To be eligible, applications (letters of expression of interest) must meet the following conditions:

- **Admissibility**: Applications must be **written in English**, submitted by the indicated deadline (see part 3) in **electronic format only**, **complete** and **signed**;
- **Administrative eligibility:** IReSP will examine the applications according to the administrative eligibility criteria, i.e. eligible managing organisations (see 5.2) and the scientific coordinator of the team must not be a member of the scientific evaluation committee, nor of the international scientific committee, nor even of a stakeholder in charge of this call;
- **Scientific eligibility:** The letter of expression of interest must meet the objectives and fall within the scope of this call (see part 2);
- **Scientific evaluation:** Each application is then evaluated by all members of the scientific evaluation committee (see 6.4) who will discuss together the quality of the applications and propose a list of teams selected to participate in the co-construction programme.

6.4. Scientific criteria for the evaluation of the expression of interest letters

Eligible and admissible letters will be evaluated based on the following scientific evaluation criteria:

Quality of the team:

- Skills of the team and, in particular, of the coordinator;
- International recognition;
- Excellent track record of publishing research;
- Quality and synergy of the proposed partnership between researchers and players in the field;
- Innovative character and relevance to what already exists;
- Complementarity of participants regarding the other applications and seeking a co-constructed project.

Teams expertise/skills:

- Scientific quality and relevance of methodologies currently used;
- Quality of expertise;
- Relevance of skills to objectives;
- Relevance of expertise/skills to the co-construction programme.
- Knowledge and access to relevant data;
- Good knowledge, and experience working with women with epilepsy (expert by experience) and strong involvement with patient organisations;
- Ability to combine skills in an extensive network.

Expected benefits of proposed research activities:

- Impact of benefits in terms of knowledge, social impact, and public health;
- Interlinkage in a larger programme.

6.5. Condition of eligibility for the final project

To be administratively eligible, the final project must meet the following conditions:

1. Only teams invited to participate in the co-construction programme will be allowed to submit a final project;
2. The scientific project coordinator must be resident in France and must belong to a French organisation (see 5.2);

The submitted project will then be evaluated by the members of the scientific evaluation committee and may be funded if the evaluation is positive.

6.6. Scientific evaluation criteria of the final project

The co-constructed project will be evaluated based on the following scientific criteria:

Scientific quality:

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

Coordinator and partner teams:

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

Methodology and feasibility:

- Methodological quality and relevance of the planned technologies;
- Suitability and justification of the co-constructed project schedule with regard to the 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.

7. Announcement of results

The results will be sent to the candidates by email. The list of selected teams will be published on the IReSP website.

After the final project submission, the result of the evaluation will be sent to the coordinator of the co-constructed project as well as to the legal representative of the organisation receiving the funding.

In addition, IReSP reserves the right to publish on its website the list of selected teams and the summary of the co-constructed project funded.

8. Contacts

For information of **scientific and administrative** aspects, please contact:

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For **technical aspects**:

- concerning EVA3: eva@inserm.fr