European Joint Programme on Rare Diseases (EJP RD)

Internal Call for Proposals 2021

Innovative Statistical Methodologies to Improve Rare Diseases Clinical Trials in Limited Populations

Call Text

Submission deadline for Proposals: 3rd of March 2021

The proposal template, Call text, submission details and further information can be found on the EJP RD website:
www.ejprarediseases.org

For any questions please contact:
innovation.callsec@ejprarediseases.org

1. MOTIVATION

There are at least 7000 distinct Rare Diseases (RD), the great majority being of genetic origin. In the European Community, EC associated states or Canada, RD are defined as diseases affecting not more than five in 10,000 persons. Although individually rare, taken together rare diseases affect at least 26-30 million people in Europe. Moreover, they represent a major issue in health care: a large number of these diseases have an early or very early onset and/or lead to a significant decrease of life expectancy. Furthermore, most of them cause chronic illnesses with a large impact on quality of life and the health care system.
The specificities of RD with limited number of patients' populations, scarcity of relevant knowledge and expertise, and fragmentation of research - single them out as a distinctive domain of very high European need.

Recent developments in the context of small population clinical trials suggest that traditional statistical methodologies to design and analyse efficient trials could not be applied to RD treatment evaluations in particular those with limited populations. Thus, there is a greater need to apply innovative statistical methodologies for RD clinical trials therapy evaluation.

In this context, the European Joint Programme on Rare Diseases (EJP RD) implements the present internal call on innovative statistical methodologies in clinical studies to foster and improve RD clinical studies in limited populations (aka innovation project).

2. AIM OF THE CALL

The call for innovation projects aims to develop innovative statistical methodologies to address unmet needs associated with the development and the analysis of clinical studies in limited populations. Necessary for a successful innovation project is to present a well-defined methodological gap in a RD area where an appropriate clinical study methodology is missing. In the context of this call, limited populations are considered as a limited patient population EU wide (number below the definition of populations in ultra-rare diseases of 1 affected in 50,000: reference DOI: 10.1186/s13023-017-0597-1), either because the disease prevalence is low or because the population is restricted to a specific disease sub-group representing only a limited number of patients.

Innovation is defined as the development of new statistical methodologies to improve rare diseases clinical studies in limited populations. It might be based on existing data (ready to use data) or data that will be finalized within the first 6 months of the project timeline. In the case of a data reuse, the data collection characteristics and how it will be used in the project should be specified and should apply ethical and regulatory requirements.

The application should address the development of innovative statistical approaches dedicated for limited populations. Application should address at least one of the pre-identified (but not limited to) promising areas:

1. Develop a disease progression model from a natural history cohort or other observational studies.
2. Develop and validate a disease specific clinically meaningful outcome with special interest in PCOMs, or composite endpoints.
3. Develop a design and analysis procedure for a pharmacometric model and/or bridging study.
4. Develop a randomization-based model as an alternative analysis strategy and explore the level of evidence. However, the applicants are encouraged to present a proposal covering additional areas in the context of limited population clinical studies where methodological challenges remain.

3. MANAGEMENT BOARDS

The Scientific Evaluation Committee (SEC) composed of internationally recognised, independent scientific experts will manage the evaluation process of the call with support of the Call Secretariat (CS) (set up at the EJP RD coordination office). SEC members must sign a confidentiality agreement and a statement to confirm that they do not have any conflicts of interest. SEC members and CS are not allowed to submit or participate in proposals within this call.

Task Force Group of WP20 (TFG) is responsible for reviewing the existing state-of-the-art for clinical study methodologies at European and international levels in specific topics related to clinical trials in rare diseases and deliver the roadmap of available methodologies promising to gain efficiency for a given RD or a group of RDs. The duties of the TFG will include the identification of promising areas for the innovative methodology projects; the contribution to call description and the writing of the final report summarizing main results of the WP20 including recommendations roadmap.

In addition, once the funded projects will be running, the Task Force Group of WP20 (TFG) with the leaders of the Task 20.4 will be supporting the monitoring of the innovation projects. TFG members and leaders of the Task 20.4 must sign a confidentiality agreement and a statement to confirm that they do not have any conflict of interest.

4. APPLICATIONS

Submission of innovation projects is limited to partners from institutions beneficiaries of the EJP RD (internal call, see 4.2).

Each proposal must be composed of a minimum of 3 eligible partners from 3 different countries, representing different expertise including at least one methodological expert but other expertise e.g. clinician, patient advocate, pharmacologist, regulator etc. are highly recommended. The involvement of industry is also encouraged when relevant. (see section 4.2 for details). Partners will have to establish a joint research consortium and assign a project coordinator for their consortium (among one of the partners). The maximum number of eligible research partners of a joint multiple partners application is
limited to 6. No more than two partners from the same country can participate in the consortium. Collaborators securing their own funding (associated partners) can also be included in the consortium (see section 4.2). It is expected that relevant considerations on budget allocation between partners will be in line with their contribution and assigned tasks (see also section “6.1 Funding model” and “6.3 Funding contracts”) during the development of the proposal.

Each proposal must nominate a project consortium coordinator among the project partner principal investigators. In the case that one PI participates in more than one proposal, he/she should not be coordinating more than 2 projects. Each consortium partner will be represented by a single principal investigator. The project coordinator will represent the consortium externally and towards the CS and TFG and will be responsible for its internal scientific management (such as controlling, reporting, intellectual property rights issues and contact with the CS and TFG).

The duration of the innovation projects will be up to 26 months.

4.1 Submission of proposals

The submission of the proposal is a one-stage process. The following process will be applied to submission of proposal:
After the official opening of the call on the 07 of December 2020, the proposers will be asked to submit their application (Full Proposal template will be provided on the EJP RD website) by 5 PM Central European Time (CET) on the 3rd of March 2021 to the Call Secretariat at: innovation.callsec@ejprarediseases.org.

Please note that only proposals using the Full Proposal template provided on the EJP RD web page (www.ejprarediseases.org) will be accepted. The proposal document must respect the format and the length indicated. Proposals exceeding these limitations will be rejected without further review.

The full proposal should include the following (minimal) information:

1. Information on the project:
   a. Project title and project acronym;
   b. Name and full affiliation of the project coordinator designated by the consortium to act as its representative;
   c. Names and full affiliations of the partners requesting funding (EJP RD beneficiaries);
   d. Names and full affiliations of the associated partners, if applicable (academia, clinical/public health sector, private companies, patient advocacy organizations);
   e. Contact information of the data owner (industry or academic owner, might come from institutions outside of EJP RD) of submitted data, if applicable;
f. Duration of the project (max 26 months);
g. Total funding applied for (€);
h. Lay summary (max. 1600 characters including spaces);

2. Description of the project (please see the instructions in the full proposal template):
   a. State of the art: State of the art: Detailed description of the methodological gap. This can be one of the topics listed in section “2. Aims of the call” or can be an additional topic. The gap description needs to summarise the state of the art of the selected methodology and its previous application to the selected clinical area as well as the methodological issues that have not previously been studied. The applicants should justify and explain their motivation to choose the specific unmet need, and present available material (e.g. “unable to investigate a research question in a specific RD due to non-existing methodology”), then present the available material (part of registry data, part of clinical trial data), explain the specific research question, how the existing methodology fails, and provide details and sources to prove the population size, registry details.
   b. A description of methodological concepts that will be utilized to tackle the identified gap and build the innovative methodology.
   c. Research Project: The proposed work as well as the aims should be related to the unmet medical and patient related needs that is addressed to show the potential health impact.
      i. Aims
      ii. Relationship of the aims to the unmet medical need, patient need and methodological gap
      iii. Research questions
      iv. Methods
      v. Expected results
      vi. Pathway to health impact
      vii. Methodological risks of the project
   d. Quality and efficiency of implementation of the proposed project.
   e. Added value of the proposed transnational collaboration.

3. Brief CV for each principal investigator including a description of the main domain of research and a list of the 5 most relevant publications within the last five years regarding the proposal (please see the instructions in the full proposal template).

4. Budget plan of the project (template of the requested budget table is present in the application form)
   a. Detailed number of person months
   b. Travel costs
   c. Consumables
5. Date and signature of the coordinator.

Note, in case previously acquired data are used to support the development within the project, a signed confirmation letter (emails will not be considered valid documents) that the consent and/or authorisation for data re-use is granted by the private owner of the data is mandatory.

4.2 Eligibility criteria for application:

1. **Only partners from institutions beneficiaries of the EJP RD are eligible to receive funding.** This includes Linked Third Parties or, parties bound by the Network Agreement with the beneficiary institution (and thus being able to integrate EJP RD project as Linked Third Party at later stage).

2. Each proposal must be composed of a minimum of 3 eligible partners from 3 different countries, representing different expertise including at least one methodological expert. The maximum number of eligible research partners for a joint multiple partners application is limited to 6.

3. Not more than 2 partners from the same country.

4. Consortia may include collaborators that secure their own funding. Collaborators cannot be project leaders, and their contribution to the research project must be described (where relevant a CV should be included in the proposal). As they do not receive funding as part of this call, they do not count toward the limit of 6 partners requesting research funding. There is no limit on the number of collaborators per country, however, the added value of the collaboration must be clearly described, and the number of collaborators must remain manageable within the limits of the project.

5. Projects shall address the statistical methodological challenges of a single or a group of **rare diseases** within limited population. There is no limitation with respect to type of treatments (molecule, device, intervention...).

If data are used to support the development of the project, please be sure to have permission from the data owner (company, health institution or other data owner) that data reuse is granted. In the case of project approval, the individual patient data will have to be anonymized and patient consent provided. In order to comply with ethics requirements on data processing please consider section 4 - **Personal Data of the Horizon 2020 Programme Guidance How to complete your ethics self-assessment** ([https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-self-assess_en.pdf](https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-self-assess_en.pdf)), and **section 6.5 Respect of relevant European and international standards** of this document.
Specific case of European Reference Networks:
At present, all 24 ERNs are involved in the EJP RD through their coordinating institution or (in exceptional cases) through one of the ERN member institutions. In order to accommodate the participation of specific members of each ERN it was agreed that they should be attached to the main ERN beneficiary as Linked Third Parties (LTP). Each identified LTP must be enumerated in the EJP RD Grant Agreement and their tasks and budget should be described. The legal connection between the main ERN beneficiary and its LTP(s) is ensured by the Network Agreement signed within each ERN and independent on their participation in the EJP RD.
In case new (not yet identified as main beneficiary or its Linked Third Party (LTP) in the GA of the EJP RD) entities will participate and will be granted in the innovation projects, it will be mandatory to amend the EJP RD Grant Agreement and identify them as LTPs with respective budget. Thus, it is mandatory that the Network Agreement is signed within each participating partner.
In case of doubts related to the current status of your ERN and your institution please contact the Call Secretariat at innovation.callsec@ejprarediseases.org

4.3 Deadline for full proposal submission

There will be a one-stage submission procedure for applications. A proposal document (in English) shall be prepared jointly by the partners of a proposal and must be submitted by the coordinator to the CS via email to innovation.callsec@ejprarediseases.org no later than 3rd of March 2021, at 5 p.m. Central European Time (CET).

All questions related to the call should be addressed to the Call Secretariat reachable at innovation.callsec@ejprarediseases.org

5. EVALUATION

5.1 Evaluation criteria for full proposals

Proposals will be assessed according to evaluation criteria that are in line with Horizon 2020 rules (see below), using a common evaluation form. A scoring system from 0 to 5 will be used to evaluate the proposal’s performance with respect to the different evaluation criteria.

Scoring system:

0: Failure: The proposal fails to address the criterion in question or cannot be judged because of missing or incomplete information.
1: **Poor:** The proposal shows serious weaknesses in relation to the criterion in question.

2: **Fair:** The proposal generally addresses the criterion, but there are significant weaknesses that need corrections.

3: **Good:** The proposal addresses the criterion in question well, but certain improvements are necessary.

4: **Very good:** The proposal addresses the criterion very well, but small improvements are possible.

5: **Excellent:** The proposal successfully addresses all aspects of the criterion in question

**Evaluation criteria:**

1. **Excellence**
   a. Clarity and pertinence of the objectives.
   b. Credibility of the proposed approach and methodology.
   c. Soundness of the concept.
   d. Competence and experience of participating research partners in the field(s) of the proposal (previous work in the field, specific technical expertise).
   e. Expected Quality of data (completeness of individual patient level data, completeness of variable list, details of other necessary information like randomization report and list, necessary for the purpose of the intended project, completeness of the supporting material).

2. **Impact**
   a. Potential of the expected results on the future clinical, public health and/or other socio-economic health relevant applications, including patients’ needs.
   b. Transferability: In case the application of the innovative statistical methodology is limited to a specific RD, the applicants are encouraged to show it values for other RD areas. Quality of the strategy for exploitation/dissemination of project results
   c. Added value of the proposed transnational collaboration

3. **Quality and efficiency of the implementation of the project**
   a. Coherence and effectiveness of the work plan (including Gantt chart, deliverables and milestones), appropriateness of the timeframe, allocation of tasks and resources (including budget) to respective partners.
   b. Feasibility of the project (adequate requested resources; access to patients or patient’s data and/or material if needed).
c. Complementarity of the participants within the consortium.
d. Appropriateness of the management structures and procedures, including risk management, contingency plans and innovation management.
e. Quality of the proposed Data Management Strategy (how clinical data will be handled during and after the project; how data will be stored and processed; which methodology for protection of data will be applied, including transfers to non-EU countries; identification of Data Protection Officer).

Evaluation scores will be awarded for the 3 main criteria, and not singularly for the different aspects listed below the criteria. Each criterion will be scored out of 5. The threshold for individual criterion will be 3. The overall threshold, applying to the sum of the three individual scores, will be 12. The maximum score that can be reached from all 3 criteria together is 15 points.

5.2 Evaluation process

Each full proposal will be allocated to at least three SEC members who fit the profile of the application. Each reviewer will individually perform the assessment of the proposals and fill the evaluation form with scores and comments for each criterion. The SEC members will meet to discuss further, assign final scores, make a classification of the proposals and establish a ranking of the proposals recommended for funding. The final summary review report will be prepared by the Call Secretariat based on the final recommendations of the SEC and transmitted to the applicants.

Ethical evaluation

Proposals will also be remotely evaluated by independent experts in ethics. These experts will report on the feasibility of a given proposal to comply with the ethical requirements. If necessary, additional tasks and documents will be requested by the ethics board from the applicants to ensure the approval of the project. Only those proposals approved by both, the scientific and ethical evaluations (complying with all central Horizon 2020 and regional/national ethical requirements), will be funded.

5.3 Funding decision

Based on the ranking list established by the SEC and the information on available funding provided by the Call Secretariat, the SEC will recommend the projects to be funded within the EJP RD WP20 - Task 20.4. If necessary, the SEC will determine a priority order for proposals, which have been awarded the same score within a ranked list. The following criteria will be applied successively for every group of ex aequo proposals requiring
prioritization, starting with the highest scored group, and continuing in
descending order:
- 1\textsuperscript{st} criterion: Proposals that address methodological topics not otherwise
  covered by more highly ranked proposals;
- 2\textsuperscript{nd} criterion: Proposals that address more than one RD (according to
  Orphanet Database Classifications);
- 3\textsuperscript{rd} criterion: Proposals that cover RD not otherwise covered by more
  highly ranked proposals (according to Orphanet Database Classifications).

After, the revision of recommended project by ethics experts, the Call
Secretariat will communicate to all project coordinators the final decisions
together with the final summary review of the evaluation from the SEC and
Ethics committee.

6. FINANCIAL AND LEGAL ISSUES

6.1 Funding model

The funded projects will benefit from the EJP RD allocated resources to task 20.4
“Innovative statistical methodologies to improve RD clinical trials in limited
populations” of WP20 “Accelerating the validation, use and development of
innovative methodologies tailored for clinical trials in RDs”. As described in
section 4 this call is internal and thus open to the partners of the EJP RD only.
The funding model of the EJP RD applies, that is all projects will be co-funded
up to 70\% and the remaining 30\% should be covered by the (in-kind)
contribution of partners participating in the project. The total EC contribution
to innovation projects will be 2 million €. It is expected to fund between 5 and
8 projects. Thus, in case a funding of 300,000 € is requested, the total cost of the
project (eligible direct costs, including in kind contribution) should be of at least
430,000 €. The financial reporting of the projects will be part of the general
annual EJP RD reporting of respective partners.

6.2 Funding contracts

Since the call is internal, there will be no specific funding contracts.
However, each funded partner will receive detailed information on final
allocated budget, the required in-kind contribution and the reporting
procedure.

Changes to the budget or to the composition of research consortia should not
occur within the lifetime of the project, unless there is a good justification. Any
minor changes have to be well justified, reported to the Call Secretariat and
will be consulted with the TFG and EJP RD administrative officer. Based on their
recommendations, the proposed changes will be integrated and reported in
the Annual Work Plan of the EJP RD (to be validated by the EJP RD General Assembly). However, in case of major changes, an independent expert can be consulted to help with the final decision. The research partner(s) shall inform the Call Secretariat immediately of any event that might affect the implementation of the project.

6.3 Research consortium agreement and ownership of intellectual property rights

Each of the innovation projects will become an integral part of the EJP RD and thus EJP RD Grant Agreement and Framework Consortium Agreement will apply. Results and new Intellectual Property Rights (IPR) resulting from projects funded through the EJP RD WP20 call for innovation projects will be owned by the projects beneficiaries’ organisations according to specific national/regional rules on IPR and as specified in the FCA. If several participants have jointly carried out work generating new IPR, they shall agree amongst themselves (FCA sections 8.1 and 8.2: As set forth under Article 26.2 of the Grant Agreement, the joint owners must agree in writing on the allocation and terms of exercise of their joint ownership in a separate agreement (“Joint Ownership Agreement”) to ensure compliance with their obligations under this Framework Consortium Agreement) as to the allocation of ownership of IPR, taking into account their contributions to the creation of those IPR as well as the relevant guidelines on IPR issues.

The results of the research project and IPR created should be actively exploited and made available for use, whether for commercial gain or not, in order for public benefit to be obtained from the knowledge created (GA article 28.1: Each beneficiary must — up to four years after the period set out in Article 3 — take measures aiming to ensure ‘exploitation’ of its results).

The EJP RD shall have the right to use documents, information and results submitted by the research partners and/or to use the information and results for their own purposes, provided that the owner’s rights are kept and taking care to specify their origin (GA articles 31.2: The beneficiaries must give each other access — on a royalty-free basis — to results needed for implementing their own tasks under the action, and 31.3: The beneficiaries must give each other — under fair and reasonable conditions (see Article 25.3) — access to results needed for exploiting their own results).

6.4 IRDiRC policies and guidelines

The aim of the call is in compliance with the vision and goals set by the International Rare Diseases Research Consortium (IRDiRC), which fosters international collaboration in rare diseases research.
The IRDiRC vision: Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention.

In order to work towards this vision, IRDiRC has set three goals for the next decade:

- **Goal 1:** All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline.
- **Goal 2:** 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options.
- **Goal 3:** Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients. For more information see IRDiRC website: [http://www.irdirc.org/](http://www.irdirc.org/)


In addition, when relevant, project partners are encouraged to consider the Orphan Drug Development Guidebook which provides an innovative and unique model to expedite the process of drug development by systematically organizing the resources and tools available for drug developers: [https://irdirc.org/orphan-drug-development-guidebook-materials/](https://irdirc.org/orphan-drug-development-guidebook-materials/).

### 6.5 Respect of relevant European and international standards

The submitted proposals have to respect relevant European and international standards like:

- **The General Data Protection Regulation (GDPR):** [the European Regulation (EU) 2016/679](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32016R0679) on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. This Regulation applies in all Member States from May 25, 2018 and thus also for the EJP RD granted “innovation projects”;
- **The FAIR principles,** to make research data Findable, Accessible, Interoperable and Re-usable (FAIR):
- The processing\(^1\) of research data during & after the end of the project;
- What data will be processed;
- Which methodology & standards will be applied;
- Whether data will be shared/made open access.

• General ethical and legal requirements: Ethics is an integral part of research. Ethics should be embedded in the research and considered from the outset, and although legal and regulatory considerations may vary across different countries, EJP RD will only fund proposals which comply with national and international ethical standards, rules and legislations.

### 7. RESPONSIBILITIES, REPORTING REQUIREMENTS AND DISSEMINATION

It is expected that the list of the funded innovation projects will be announced by September 2021. To maximise the impact of funded projects the TFG with leaders of task 20.4 will be engaged in their monitoring. To that end dedicated conference calls (or meetings if required) will be organised every six months allowing close interaction between the projects and the TFG but also ensuring the possibility to connect to additional expertise or support that would be required by the projects.

The coordinators of all funded projects must submit a short scientific report at the start of every calendar year (January), in line with the reporting calendar of the EJP RD; and a financial report within the 2 first months of each calendar year – again in line with the financial reporting calendar of the EJP RD. The scientific project report should foresee a section dedicated to the ethical and regulatory issues management. Within three months of the end of the innovation projects, the coordinators must submit a final scientific project report. Research partners are jointly responsible for the delivery of the reports, and only reports delivered on behalf of the consortium, via the project coordinator, will be accepted.

The results will be communicated to the Call Secretariat who will take in charge the follow up with respective bodies

- Coordination of the EJP RD;
- Pillar 4 – Task 20.1, TFG, Task 20.2 partners: “Support in design and planning of RD clinical studies”;

\(^1\) According to the GDPR definition: processing means any operation or set of operations which is performed on personal data or on sets of personal data, whether or not by automated means, such as collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction
• Pillar 3 – WP18 partners: “Development and adaptation of training activities”;
• WP5 – communication manager of the EJP RD.

Each beneficiary must ensure open access (free of charge, online access for any user) to all peer-reviewed scientific publications relating to its results if this is compliant with national/regional funding regulations. **The budget for publication should be accounted in the budget of each project.**

Beneficiaries must ensure that all outcomes (publications, etc.) of EJP RD projects include a proper acknowledgement of EJP RD. This includes the display of the EJP RD logo when possible.

Beneficiaries must also include credits according to national/regional rules, where applicable (for in kind contributions).

In addition, as specified under EJP RD Grant Agreement N°825575, unless the EC requests or agrees otherwise or unless it is impossible, any dissemination of results (in any form, including electronic) must:
• display the EU emblem;
• include the following text:
  “This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575”;
• when displayed together with another logo, the EU emblem must have appropriate prominence.

For the purposes of the obligations under this Article, the beneficiary may use the EU emblem without first obtaining approval from the Agency. This does not however give it the right to exclusive use. Moreover, the beneficiary may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

**8. CONTACT AND FURTHER INFORMATION**

[www.ejprarediseases.org](http://www.ejprarediseases.org)

**Secretariat of the call:**
innovation.callsec@ejprarediseases.org