European Joint Programme on Rare Diseases (EJP RD)

Internal Call for Proposals 2019

Demonstration projects on existing statistical methodologies to improve RD clinical trials

Call Text

Submission deadline for Proposals: 15th of May 2020

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:

demonstration.callsec@ejprarediseases.org

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1. MOTIVATION

There are at least 7000 distinct Rare Diseases (RD), the great majority being of genetic origin. 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 - limited number of patients per disease, scarcity of relevant knowledge and expertise, and fragmentation of research - single them out as a distinctive domain of very high European need.

Recent developments suggest that traditional statistical methodologies to design and analyse efficient trials could not be applied in general to RD treatment evaluations as required. Thus, there is a greater need to apply innovative statistical methodologies for clinical trials for therapy evaluation to RDs.

In this context, the European Joint Programme on Rare Diseases (EJP RD) implements the present internal call for demonstration projects to evaluate existing innovative statistical methodologies to improve RD clinical trials.

During the last 5 years, three unique EU funded projects asterix, IDeAl, and InSPiRe, developed innovative statistical methodologies to improve the design and analysis of small population clinical trials aimed at efficient evaluation of novel therapies useful in rare diseases research. Most of the developed methods are evaluated from the methodological point of view, but not applied to specific RD problems yet. Thus, the scientific RD community including stakeholders such as patient advocacy groups, regulators and clinicians have difficulties to understand the value of these innovative methodologies for their research.

The Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (asterix) project developed design and analysis methodologies for single trials and series of trials in small populations, including patient-level information and perspectives in design and decision making throughout the clinical trial process and new methods for regulatory purposes.

- asterix:
    - http://www.asterix-fp7.eu/

The Integrated Designs and AnaLysis of small population clinical trials (IDeAl) project addressed the challenges implied by the Committee for Medicinal Products for Human Use (CHMP) regulatory guidance (CHMP. Guideline on clinical trials in small populations. [Online] 2007. [Cited: February 1, 809 2013.], www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf) within nine scientific work-packages: adaptive design, biomarkers, decision theory, extrapolation, genetic factors, optimal design, pharmacogenetics, randomisation and simulation. A toolbox with a huge number of options to improve the design and analysis as well as a comprehensive recommendation paper is available.

- IDeAl:
    - https://www.ideal.rwth-aachen.de/

The Innovative Methodology for Small Populations Research (InSPiRe) project addressed two broad areas efficient study design and improved analysis including evidence synthesis. This includes approaches for targeted treatment trials, new decision-making methods for small population clinical trials, and

improved robust meta-analysis methods for a small number of trials and on early phase clinical trial design including extrapolation from adult to paediatric studies.

- InSPiRe:
  - https://warwick.ac.uk/fac/sci/med/research/hscience/stats/completedprojects/inspire/

2. AIM OF THE CALL

The call for demonstration projects aims to show the usability and capability of the innovative statistical methodologies for clinical trials in rare diseases, which have not been demonstrated on existing data for specific rare disease clinical trials yet. Necessary for a successful demonstration project is the collection of sufficient data from a rare disease clinical trial and related information to enable demonstration of the practicability, performance and opportunities of the innovative methodologies applied to these already acquired data. Trials are often performed with standard classical methodologies not specific for rare diseases resulting in a loss of power to show positive effects.

The demonstration projects should use one of the following nine innovative statistical methodologies

1. Uncertainty evaluation (bias assessment)
2. Primary outcome variable (surrogate)
3. Primary outcome variable (co-primary)
4. Use of external information (historical control)
5. Use of external information (extrapolation)
6. Use of external information (dose response profiles)
7. Use of external information (single arm trials – threshold crossing)
8. n-of-1 trials
9. Rigorous use of longitudinal information, linked to an **existing** clinical trials dataset for a specific rare disease.

The details of data needed to demonstrate the above listed methodological topics are described in section "4.3 Further information".

Projects may concern a group of rare diseases or a single rare disease following the European definition of a rare disease i.e. a disease affecting not more than five in 10.000 persons in either the European Community, EC associated states or Canada.

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 demonstration projects and innovative methodology projects; the preparation of detailed internal call description for the demonstration projects and the writing of the final report summarizing main results of the WP20 including recommendations roadmap.

Once the funded projects will be running, the Task Force Group of WP20 (TFG) will be in charge of the monitoring of the demonstration projects. TFG members must sign a confidentiality agreement and a statement to confirm that they do not have any conflict of interest.

4. APPLICATIONS

Submission of demonstration projects is limited to **partners from institutions beneficiaries of the EJP RD**. 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).
In addition, each proposal must include one of the methodological experts matching the expertise for methodologies identified under section 4.3 Table 1.

IMPORTANT: The applicants are asked to NOT to engage with any statistical experts and elaborate statistics plan until the preparation of full proposal.

The list of eligible methodology experts that will accompany the projects (and were identified in advance by the Task Force Group as the best experts to fulfil the objectives of this call) will be provided only on the 31st of March 2020 to avoid any potential Conflict of Interest and privilege any proposal over the other (please see further instructions below). A partnership with one of these experts is mandatory to efficiently prepare the **full** proposal.

Thus, each **full** proposal must be composed of a minimum of two research partners: a clinician and one of the indicated methodological experts. However, demonstration project proposals may involve multiple partners provided that both statistical and non-statistical expertise is included (see section 4.2 for details). In case of joint multiple partner applications, partners will have to establish a joint research consortium and assign a project coordinator for their consortium (among one of the partners). There is no

limitation regarding the geographical distribution of research partners. The maximum number of research partners of a joint multiple partners application is limited to 10. No more than two partners from the same country can participate in the consortium (excluding future methodologist to be assigned to the project).
It is expected that in case of multiple partners involved in the project relevant considerations on budget allocation between partners will be taken into account (see also section "6.1 Funding model" and "6.3 Funding contracts") during the development of full proposal. Budget repartition and detailed allocation to the participating partners will not be requested in the Phase 1 (see below).

Each **full** 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 demonstration projects can be **up to 24 months**.

4.1 Submission of proposals

The submission of proposal will follow two-phase process.
Phase 1:
After the official opening of the call on the 1st of February 2020, the proposers possessing suitable data sets will be asked to submit only 1-pager (template will be provided) by 5 PM Central European Time (CET) on the 15th of March 2020 to the Call Secretariat at: demonstration.callsec@ejprarediseases.org.

This stage will serve ONLY to review available data and ideas, and subsequently propose matching experts in methodology. It is not necessary to identify your methodologists in advance of this stage!

All 1-page applications will be gathered by the Call Secretariat and submitted to the group of methodologists that will accompany the projects (and were identified in advance by the Task Force Group as the best experts to fulfil the objectives of this call).
The methodology experts will review all applications and issue recommendations including the most suitable methodology and matching expert to develop the project. The recommendations and contact details of respective methodologists will be communicated to the applicants on the 31st of March 2020.

IMPORTANT: Phase 1 is not an evaluation process! It will serve only to provide the best recommendations on the methodologies that can be explored with proposed data sets and relevant expertise from methodology experts to be included in the full proposal.

Phase 2:
The applicants with matching methodologists will be asked to submit full proposals.
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:

- Project title and project acronym;
- Name and full affiliation of the project coordinator designated by the consortium to act as its representative;
- Names and full affiliations of the principal investigators participating in the project;
- Contact information of the company that owns submitted data, if applicable;
- Contact information of the patient organisation representative, if applicable;
- Confirmation letter that the consent and/or authorisation for data re-use is granted by the private owner of the data, if applicable. A template of this letter will be provided with call documents and must be completed and signed by the respective owner;
- Duration of the project (months);
- Total funding applied for (€);
- Lay summary (max. 1600 characters including spaces);
- Description of the project (once converted into Pdf document: max. 5pages DIN-A4, Arial font 11, single-spaced, and margins of 1.27 cm) including:

a. Definition of the disease area, e.g. Rare epilepsy, neurology, metabolic diseases, etc.;
b. For the suitability of the data, a description which of the Methodological topics formulated in section 4.3, Table1 the applicants aim to fulfil with the submitted data;
c. Description of bottlenecks encountered in previous clinical trials analysis;
d. When applicable, attach at least the initial trial protocol accompanied with at least one of the following documents:
    a. The trial statistical analysis plan (TSAP);

   b. The data management and validation plan (DMVP);
   c. Reference in clinical trial gov or in EU database;
   d. Publications in peer-reviewed scientific journals (listed in Web of Science) about the design and/or trial findings

e. Unmet medical and patient need that is addressed by the proposed work and the potential health impact that the results of your proposed work will have;
f. Quality and efficiency of implementation;
g. Added value of the proposed transnational collaboration.

- Budget plan of the project (template of the requested budget table is present in the application form)
- 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 (once converted into Pdf document: max. 1 page DIN-A4; Arial font 11, single-spaced, margins of 1.27 cm per principal investigator).
- Date and signature of the coordinator.

4.2 **Eligibility criteria** for application:

1. **Only partners from institutions beneficiaries of the EJP RD are eligible**. 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. In addition, each proposal must include one of the methodological experts identified under section 4.3 Table 1.
3. Not more than 2 partners from the same country (excluding methodologist to be assigned to the project)
4. Projects shall involve data from **rare diseases** (a group of rare diseases or a single rare disease following the European definition) related clinical trials. There is no limitation with respect to type of treatment (molecule, device, intervention…).
5. Availability of data: Existing data from clinical trials that were complete, i.e. completed enrolment, lock of database, and published final study report. **Consequently, projects based on data of trials currently recruiting patients or ongoing are NOT eligible.** External data e.g. control groups from other trials or registries can be annotated to the clinical trial data for evaluation of some specific methods. Data from pre-terminated trials, e.g. after final decision based on interim analysis or terminated for other reasons, not reaching their study goal are eligible, as long as the trial is completed with respect to patient enrolment, database lock, and final study report.
6. Suitability of data: The data should fit at least one of the methodological topics described in section 4.3, Table1. Generally, the data should belong

to an interventional trial. For most methodologies, data need to be from one or more randomized clinical trials with at least two parallel treatment groups. Furthermore, the data should always include individual (pseudonymised) patient data (potentially with the randomization scheme) with at least one potential endpoint variable (among others: longitudinal, potential surrogates and co-primary endpoints may be eligible), pseudonymised medicinal product names are eligible;

- where applicable, data of "control groups" from a registry or other randomized clinical trials can be annotated;
- where applicable, dose response profile patient's data.

Please note that:

- all trial phases are eligible;
- single arm trials are not excluded (see section 4.3., Table 1).

The aim of this demonstration call is not to reanalyse or question the original analysis of data from randomized controlled clinical trials, where efficacy was established, but rather to re-evaluate data that lacked efficiency because it was analysed with classical statistical methodology, which might be not feasible for trials in the rare disease context.

If the data is owned by a company please be sure to have permission from the owner (Permission letter is required), that in case of approval for this project, the patient anonymized individual data can be used and shared for reanalysis in the context of the demonstration project and according to the subjects' consent.

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). In particular, it is important to check if the authorisations for data re-use have been obtained from patients.

4.3 Further information

Details of the experts and the data needed for the eligible methodological topics (see Section 2) are given in the following table.

Table 1. Description of data required for each methodological topic

Methodological topic ***[qualified stat. experts, affiliation, country]***	**Data needed to demonstrate methodology**

Methodological topic ***[qualified stat. experts, affiliation, country]***	**Data needed to demonstrate methodology**
Uncertainty evaluation	• Patient individual data **AND** • 2 or more, 2-arm parallel group randomized controlled clinical trial **AND** • Randomization scheme
Primary outcome variable (Surrogate)	• Patient individual data **AND** • One true endpoint with several candidates of surrogate endpoints **AND EITHER:** • Several 2-arm parallel group randomized controlled trials comparing the same treatments **OR** • At least one multicentre 2-arm parallel group randomized controlled trial
Primary outcome variable (Co-primary)	• Patient individual data **AND** • 2-arm parallel group randomized controlled clinical trial **AND EITHER:** • 2-3 co-primary (continuous or binary) endpoints **OR** • 2-3 secondary (continuous or binary) endpoints
Use of external information (Historical control)	• Patient individual data **AND** • 2-arm parallel group randomized controlled clinical trial with one continuous endpoint **AND EITHER:** • Patient individual historical control data **OR** • Patient individual registry data

Methodological topic ***[qualified stat. experts, affiliation, country]***	**Data needed to demonstrate methodology**
Use of external information (Extrapolation)	• Patient individual data **AND** • 2-arm parallel group randomized controlled clinical trial in a source (large)population **AND** • 2-arm parallel group randomized controlled clinical trial in a target (small)population **AND** • Same study design including treatments and hypotheses in both trials (to test the assumption of extrapolating from the source to the target population)
Use of external information (dose response profiles)	• Dose response profiles **AND** • 2-arm parallel group randomized controlled clinical trial in a source (large)population **AND** • 2-arm parallel group randomized controlled clinical trial in a target (small)population
Use of external information (single arm trials – threshold crossing)	• Patient individual data **AND EITHER:** • Single-arm clinical trial **OR** • Single-arm clinical trial and corresponding 2-arm parallel group randomized controlled clinical trial
n-of-1 trials	• Patient individual data **AND** • a series of n-of-1 trials
Rigorous use of longitudinal information	• Patient individual data **AND** • 2-arm parallel group randomized controlled clinical trial with longitudinal measured outcome data

Further details about the different topics and developed methodologies can be found in the scientific publications listed in the following summary publications:

- Hilgers, R.-D.; Bogdan, M.; Burman, C.-F.; Dette, H.; Karlsson, M.; König, F.; Male, C.; Mentre, F.; Molenberghs, G.; Senn, S.: **Lessons learned from IDeAl – 33 recommendations from the IDeAl-net about design and analysis of small population clinical trials.** Orphanet Journal of Rare Diseases (2018)

13:77.
https://doi.org/10.1186/s13023-018-0820-8

- Friede, T.; Posch, M.; Zohar, S.; Alberti, C.; Benda, N.; Comets, E.; Day, S., Dmitrienko, A.; Graf, A.; Günhan, B.K.; Hee, S.W.; Lentz, F.; Madan, J.;Miller, F.; Ondra, T.; Pearce, M.; Röver, C.; Toumazi, A.; Unkel, S.; Ursino, M.; Wassmer, G.; Stallard, N.: **Recent advances in methodology for clinical trials in small populations: the InSPiRe project.** Orphanet Journal of Rare Diseases (2018) 13:186.
https://doi.org/10.1186/s13023-018-0919-y

- Mitroiu, M.; Rengerink, K.O.; Pontes, C.; Sancho, A.; Vives, R.; Pesiou, S.; Fontanet, J.M.; Torres, F.; Nikolakopoulos, S.; Pateras, K.; Rosenkranz, G.; Posch, M.; Urach, S.; Ristl, R.; Koch, A.; Loukia, S.; van der Lee, J.H.; Roes, K.C.B.: **Applicability and added value of novel methods to improve drug development in rare diseases.** Orphanet Journal of Rare Diseases (2018) 13:200.
https://doi.org/10.1186/s13023-018-0925-0

4.4 Deadline for full proposal submission

There will be a one-stage submission procedure for applications. A proposal document (in English) shall be prepared by the partners of a proposal, and **must be submitted by the coordinator to the CS via email to** demonstration.callsec@ejprarediseases.org **no later than May 15th 2020, at 5 p.m. Central European Time (CET).**

All questions related to the call should be addressed to the Call Secretariat reachable at demonstration.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 (of proposed work) on the future clinical, public health and/or other socio-economic health relevant applications, including patients' needs; demonstration of the reanalysis potential impact for the particular RD and potential transfer of the results to other RDs → Does reanalysis provides an important step for future research in the specific disease field?
    b. Transferability: Does reanalysis provides an important solution for research in similar RDs or RD-groups? The application should not be only limited to a very specific disease; the application should show the value to rare disease stakeholders, e.g. patient representatives and patient organisation, industry (when appropriate/applicable/available); the data of the application may be useful for more than one of the above mentioned statistical methodologies.
    c. Quality of the strategy for exploitation/dissemination of project results
    d. Added value of the proposed transnational collaboration

3. Quality and efficiency of the implementation
    a. Coherence and effectiveness of the work plan (including Gantt chart, deliverables and milestones), appropriateness of the time-frame, 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);
    c. Complementarity of the participants within the consortium in the case multiple EJP RD partners perform a joint application;
    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 of full proposals

Each full proposal will be allocated to at least two SEC members who fit the profile of the application. Each reviewer will 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, a list of those tasks that need to be done and documents that need to be submitted by the applicant partner(s) in order to receive the approval for funding from the ethical point of view will be provided. 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 select the projects to be funded by the EJP RD WP20 - Task 20.3.
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:

- Proposals that address diseases not otherwise covered by more highly-ranked proposals,
- Proposals that address methodologies not otherwise covered by more highly ranked proposals.

The Call Secretariat will communicate to all project coordinators the final decisions together with the final summary review of the evaluation from the SEC.

6. FINANCIAL AND LEGAL ISSUES

6.1 Funding model

The funded projects will benefit from the EJP RD allocated resources to task 20.3 "Demonstration projects on existing statistical methodologies to improve RD clinical trials" 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 EC contribution to demonstration projects will be up to 220,000 € per project excluding indirect costs. Thus, in case if the maximum funding of 220 000 € is requested, the total cost of the project (eligible direct costs, including in kind contribution) should be of at least 315 000 €. The financial reporting of the projects will be part of the general annual EJP RD reporting of respective partners.

6.2 Involvement of partners

Specific case of methodology experts:
As the demonstration projects aim to demonstrate the application of the innovative trial methodologies proposed by the three EU funded FP7 projects asterix, IDeAl, and InSPiRe, their unique expertise is needed to ensure the

success of the submitted projects. However, not all experts' institutions are at present beneficiaries of the EJP RD programme. Since the inclusion of experts is mandatory for each project, it is foreseen that respective institutions will be integrated in the EJP RD consortium and subsequently bound by the Grant Agreement (GA) and Framework Consortium Agreement (FCA) of the EJP RD. To complete this action, an amendment to the GA and FCA will be initiated by the coordination immediately after the evaluation and final selection of the demonstration projects.
In this context, the new Beneficiary involvement will fall under Work Package 20 "*Accelerating the validation, use and development of innovative methodologies tailored for clinical trials in RDs*" and the internal funding rate applicable shall be seventy per cent (70%). Therefore, the new Beneficiary will have to bring an in-kind contribution of thirty per cent (30%).

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 LTP in the GA of the EJP RD) ERN entities will participate and will be granted in the demonstration 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 ERN.
In case of doubts related to the current status of your ERN and your institution please contact the Call Secretariat at demonstration.callsec@ejprarediseases.org

6.3 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 requested in kind contribution and the reporting procedure.

Changes to the budget or to the composition of research consortia cannot occur within the contract/grant agreement, 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. Based on the recommendation from the TFG, 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.

6.4 Research consortium agreement and ownership of intellectual property rights

The consortium partners have to sign a consortium agreement (CA) for cooperation. For reference, see the DESCA 2020 Model Consortium Agreement (http://www.desca-2020.eu/). It is recommended that the research consortium signs the CA before the official project start date, and in any case the CA should be signed early during the lifetime of the project. Please note that national/regional regulations may apply concerning the requirement for a CA (please contact your national/regional contact point or check the country-specific information in the guidelines). Upon request, this consortium agreement must be made available to the TFG.

Each of the demonstration 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 internal call for demonstration project 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*).

6.5 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/
The project partners are expected to follow IRDiRC policies and guidelines. For more information, see http://www.irdirc.org/.

6.6 Respect of relevant European and international standards

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

- The new European Regulation (EU 2016/679) 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 "d*emonstration projects*" (https://publications.europa.eu/en/publication-detail/-/publication/3e485e15-11bd-11e6-ba9a-01aa75ed71a1/language-en)

- European Research Council Guidelines on Implementation of Open Access to Scientific Publications and Research Data (referred to in http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/open-access_en.htm)

- To make research data findable, accessible, interoperable and re-usable (FAIR), a data management strategy is mandatory in the proposal. For an example of questions for a data management strategy, see Annex 1 in http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf .

A data management strategy/plan should include information on:

- 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: according to H2020 rules, the EJP RD expects applications to fulfil ethical and legal requirements. Ethics is an integral part of research. Please consider that you have to comply with the European rules and with all the applicable country-specific laws and ethical requirements that may vary across different countries. Special attention will be paid to potential ethical issues (e.g. research on humans or animals; privacy of data and biomaterials; informed consent; secondary use of data; etc.). Only projects that fulfil the legal and ethical international/EU and national and institutional standards will be funded.

7. RESPONSIBILITIES, REPORTING REQUIREMENTS AND DISSEMINATION

The final results of the demonstration projects will be expected after 24 months (2 years) working period following the date on the funding allocation. The projects are expected to start October 1st 2020.

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 six months of the end of the project, the coordinators must submit a final scientific project report in the form of a scientific publication in a peer reviewed journal listed in Web of Science. The research partners are jointly responsible for 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";
- Pillar 3 – WP18 partners: "Development and adaptation of training activities";

[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

- 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

Secretariat of the call:
demonstration.callsec@ejprarediseases.org